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Symposium on Sulfanilamide Therapy

SULFANILAMIDE

NO THERAPEUTIC agent has appeared on the medical horizon for many years which has attracted so much attention and interest as sulfanilamide.

The few brief published preliminary reports of its use are literally amazing. If the test of time bears out these early promises, it will rank among the great therapeutic advances. As yet, however, its use must be looked upon as experimental. Conversation and correspondence have shown that within the last six months it is being used experimentally in a large number of conditions and in practically every pediatric clinic in America; further, that it is being used widely and indiscriminately in private practice. One of a number of manufacturers of the drug had orders in May amounting to four times the amount of the total orders for the four previous months. As yet little is known of its dangers and limitations. The very nature of the conditions for which it is being used as yet preclude any one clinic from reporting a sufficiently large series of cases upon which a careful and critical judgment of its value may be expressed. It is only upon such a basis, with the confirmation of the results by other independent clinical investigations, that a final judgment can be made.

Nevertheless, because of its widespread use and the tremendous interest in sulfanilamide that has been aroused in the last few months, the Editorial Board felt that THE JOURNAL OF PEDIATRICS could perform a service by exchanging the "experience to date" of a group of pediatric clinics, and making this information available to all pediatricians and hospitals for children. With this end in view a group of clinics were invited to report on their experience with sulfanilamide up to June 10, 1937. Reports from 11 hospitals and clinics follow, totaling approximately 350 cases in which sulfanilamide has been used. It is to be clearly understood that the group of reports which follow simply give the experience of the different clinics. No final conclusions are drawn. It is hoped

by the exchange of this early experience that some leads will be obtained as to its value, its limitations, its dangers, and of the various clinical conditions for which it is seemingly indicated and warrants further trial. The clinics have cooperated with the clear understanding that they are not passing judgment, nor are advocating its widespread use on the basis of the results so far obtained. We wish to express our indebtedness and thanks to the clinics taking part in this exchange of experience.

A brief summary of the pharmacology of sulfanilamide precedes the reports of the clinics.

The Editors.

THE PHARMACOLOGIC BASIS FOR SULFANILAMIDE THERAPY

ARNOLD DEM. WELCH
ST. LOUIS, MO.

IN THE following, a brief review of the pharmacologic basis for the use of the new drug, sulfanilamide, is presented. However, no attempt has been made to include every paper which might be considered to bear upon the subject.

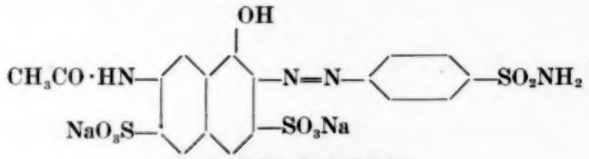
The discovery of the therapeutic activity of drugs related to para-aminobenzenesulfonamide appears to constitute a major advance in the science of chemotherapy. The introduction of these therapeutically active compounds for the treatment of streptococcal and other refractory infections has been welcomed enthusiastically by clinical medicine.

The manner in which *sulfanilamide* (para-aminobenzenesulfonamide, sulfamidyl, streptocide, prontylin, etc., $H_2N-C_6H_4-SO_2NH_2$) has been developed forms a story worth recounting. As early as 1913 Eisenberg observed that certain azo dyes possess considerable bactericidal action in vitro and considered the possibility of the application of chrysoidin ($H_2N-C_6H_3(NH_2)-N=N-C_6H_5$) to therapeutics. The sulfonamide grouping was first incorporated in azo dyes by Hörlein and associates about twenty-five years ago; it was noted at that time that the ability of these dyes to enter into intimate combination with wool proteins is greater than with similar dyes free from sulfonamide. The observations of Domagk (1935) with the sulfonamide-azo dyes on mice infected with hemolytic streptococci dramatically shifted the test object, however. In cooperation with the chemists, Mietzsch and Klarer, Domagk (1936) studied the bactericidal action of azo dyes, of which prontosil is one of the most active. Domagk's work with animals has been either partially or completely confirmed by Levaditi and Vaisman (1935), Nitti and Bovet (1935), Hörlein (1936), Colebrook and Kenny (1936) and Long and Bliss (1937).

$HCl \cdot H_2N-C_6H_3(NH_2)-N=N-C_6H_4-SO_2NH_2$

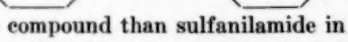
Prontosil

From the Department of Pharmacology, Washington University, St. Louis.



Prontosil—S (soluble)

Many compounds, related to the prontosils, of more or less toxicity and complication of structure have been investigated; however, Tréfouël and his coworkers (1935) and Buttle and his associates (1936) soon obtained indications that para-aminobenzenesulfonamide, a part of the prontosil molecule, is the pharmacologically effective portion. Colebrook and Kenny (1936) and Cooper, Gross and Mellon (1937) consider sulfanilamide (para-aminobenzenesulfonamide) even more efficacious than its more complicated predecessors. Indeed, it appears established (Colebrook and his associates, 1936; Bliss and Long, 1937; Fuller, 1937) that sulfanilamide is formed from prontosil by reduction in vivo. Bliss and Long have shown that the amino acid, cysteine (which possesses a high reduction potential) produces an activation of prontosil sufficient to be demonstrated in vitro as well as in vivo and is of an order comparable to that which would be expected if sulfanilamide were formed. Finally, Fuller has accomplished the isolation of sulfanilamide from the urine of patients receiving prontosil therapy. These observations doubtless account for the fact that prontosil is essentially inactive in vitro.

It is interesting to note that the sulfonamide grouping is apparently not essential to an action resembling that of sulfanilamide. Buttle and his associates (1937) have investigated certain compounds related to sulfanilamide but which do not contain the sulfonamide grouping. One of these, 4:4′ diaminodiphenylsulfone, is claimed to be considerably more active than sulfanilamide but is more toxic to mice. Another, 4:4′ dinitrophenylsulfone, is as active as sulfanilamide but is less toxic. However, undesirable side actions are produced which are absent with sulfanilamide therapy. The symptoms produced by these sulfones are also very much more persistent than are those of sulfanilamide. It has been reported (Rosenthal and his coworkers, 1937) that *di-sulfanilamide* (para-aminobenzene sulfonyl para-aminobenzenesulfonamide; 

) is a somewhat more effective compound than sulfanilamide in the treatment of streptococcic infections in mice. Of particular importance is the finding that the new compound has an acute toxicity of not more than one-fifth that of sulfanilamide. No symptoms are produced with 8 gm. per kilogram, while the maximum tolerated dose of sulfanilamide (in this strain of mice) is about 1.5 gm. per kilogram. Di-sulfanilamide is of low solu-

bility, and poor absorption from the alimentary tract is believed to explain the finding that its maximum action is exerted only on subcutaneous injection.

It is interesting to note the variety of organisms which the reports of clinical trials indicate is susceptible to sulfanilamide therapy. Infectious agents which appear to be affected by the drug are β-hemolytic streptococci, meningococci, pneumococci, gonococci and probably other species of microorganisms, e.g., certain bacterial species not belonging to the cocci. It appears that sulfanilamide is relatively ineffective against α-hemolytic streptococci. This is noteworthy since it has been stated (Garrod, see Hörlein, 1936) that neoarsphenamine, which has a demonstrable action on certain streptococci in blood, is also without effect on *Streptococcus viridans*.

In the original experiments of Domagk a virulent strain of *Streptococcus hemolyticus* derived from a human subject was employed. Control mice, when injected with 0.3 c.c. of a diluted culture, usually died within twenty-four hours. When the animals were injected with from one-tenth to one-fiftieth of the tolerated dose of prontosil, curative effects were exerted, and, if the injections were continued for from three to five days, the majority of the animals recovered.

It is not necessary to review all the work which has been carried out in the study of the action of prontosil and of sulfanilamide in the therapy of experimentally produced streptococcal, meningococcal, pneumococcal, and other infections in various laboratory animals. The investigations of Long and Bliss (1937), Colebrook, Buttle and coworkers (1936-37), Rosenthal and associates (1937), Proom (1937), and of Raiziss and coworkers (1937) are of particular interest in establishing by animal experimentation the remarkable effects of sulfanilamide. Colebrook, Buttle and O'Meara (1936) have shown that sulfanilamide is extremely active in vitro as well as in vivo; human defibrinated blood infected with streptococci to which sulfanilamide was added (1:13,000 and 1:18,000) was free from the streptococci in two days, while in control bloods a distinct increase in the number of organisms occurred in from ten to twenty-four hours. Similar results were obtained in serum. It is interesting that such striking results were not obtained in the blood of mice, guinea pigs or rabbits. These observations assume considerable significance in view of the findings of Marshall and his associates (1937) that concentrations between 1:5,000 and 1:10,000 can be attained and maintained in human blood in vivo. Proom's work establishes the protective action of sulfanilamide in experimental meningococcal infections in mice; Rosenthal and associates' observations are of similar significance in the case of pneumococci (Types I, II, and III). Raiziss and his coworkers (1937) have found that approximately one-quarter of the maximum tolerated dose is necessary to produce a

curative effect in their strain of mice infected with a very virulent strain of β-hemolytic streptococci. They point out that large doses will have to be given to patients in order to assure a cure.

The mechanism of action of sulfanilamide is at present unknown, but many have advanced hypotheses to account for its effects. Levaditi and Vaisman (1935) suggest that the drug acts by preventing capsule formation, while Long and Bliss (1937) suggest that the phagocytic activity of the polymorphonuclear leucocytes and monocytes is concerned. In vitro experiments showed that the multiplication of hemolytic streptococci is inhibited by sulfanilamide, but the authors believe that, although this may also occur in vivo, the streptococci must also be damaged to permit the marked degree of phagocytosis. Gross, Cooper, and Peebles (1937) and Weinberg, Mellon, and Shinn (1937), however, have found no indications of increased phagocytosis in animals treated with sulfanilamide. Suggestions as regards a possible rôle of the reticuloendothelial system appear to have been rendered unlikely by the finding of Gross, Cooper, and Peebles (1937) that splenectomized mice are protected to the same degree as are normal animals.

It would appear that sulfanilamide has a direct action on certain bacteria, in some way preventing their rapid multiplication and enabling the normal bodily defense mechanisms to cope adequately with the invading organisms. The earlier observations, previously mentioned, as regards the more intimate combination of prontosil-like dyes with wool proteins when the sulfonamide grouping is present are suggestive. Possibly the sulfonamide grouping is involved in the combination between the drug and constituents of the bacterial cell essential for life or reproduction.

The absorption and excretion of sulfanilamide has been the subject of a very valuable study by Marshall and his associates (1937), who developed a simple method for its determination in body fluids. The method is based on the diazotization of the compound and coupling with dimethyl-α-naphthylamine to produce a dye which can be estimated colorimetrically. It was found that sulfanilamide is excreted in the urine by the rabbit and human being partly in the acetylated form, para-acetylamino-benzene sulfonamide, a compound which is almost inactive; dogs, however, appear to excrete the substance unchanged.

It is particularly important to point out that Marshall and his coworkers found that subcutaneous administration of sulfanilamide does not lead to a higher blood concentration than when given by mouth. The absorption from the intestinal tract appears to be complete within three to five hours. It was found that, following the administration of a given daily amount of the drug in divided doses, from two to three days are required to establish equilibrium between the amount of drug injected and the amount excreted. Similarly, from two to three days

are required to free the system of the compound. As might be expected, patients with impaired renal function do not require doses as large as normal individuals to raise the blood concentration to any given level and require longer periods to clear the body of the substance. The authors suggest the possibility that sulfanilamide may be a more delicate test of kidney function than substances now in use.

These workers demonstrated the presence of the drug in saliva, pancreatic juice, bile and cerebrospinal fluid. In the latter it is present in a concentration only slightly lower than in the blood within a few hours of administration by mouth, an observation of great significance in the treatment of infections of the meninges.

It is apparent from experiments on mice infected with β-hemolytic streptococci that the maximum curative effect of sulfanilamide is exerted by maintaining a high concentration in the blood and tissues for several days. That too early withdrawal of the drug may result in a fatal relapse, following an initial favorable effect, has been demonstrated experimentally by numerous investigators. Marshall and his associates conclude that the concentration in the blood (and thus in the tissues) from a single dose will depend on (1) the dose per unit of body weight, (2) the rate and completeness of absorption from the intestinal tract, (3) the distribution ratio of the drug in the body, (4) the efficiency of the kidneys in excreting the drug, and (5) the amount of the drug present in the body in conjugated form (inactive). When the drug is given in small doses every few hours for several days, the efficiency of the renal function of the individual will be the important factor determining the concentration in the blood. Since the absorption is apparently complete, or nearly so, in man in about four hours, Marshall and his coworkers point out that a four-hour interval between doses would appear to be indicated. A single large dose could be given if it is desired to effect quickly a high blood concentration and could be followed after six to eight hours by the usual dose every four hours in order to maintain the high concentration.

From the work of Marshall and his associates (1937) it may be appreciated that sulfanilamide is not an acutely toxic drug. Buttle and his coworkers (1936) have shown that sulfanilamide is tolerated in 2.5 gm. per kilogram doses when given by mouth to mice; this dose can be repeated daily in mice infected with streptococci. Raiziss and his associates (1937) have recently investigated in mice the toxicity of sulfanilamide used subcutaneously; in rats and rabbits, intravenously; and in rabbits, orally. The maximum tolerated dose in mice (subcutaneously) was found to lie between 2 and 2.5 gm. per kilogram. The maximum tolerated dose could not be determined in rats and rabbits by the intravenous route because of the limited solubility of sulfanilamide, but doses of 0.4 gm. per kilogram and 0.2 gm. per kilogram were

given the rats and rabbits, respectively. A large number of experiments was performed on rabbits which received the drug via the stomach tube. It was found that a dose of 2 gm. per kilogram kills 50 per cent of the animals, 2.5 gm. per kilogram is lethal, but 1.5 gm. per kilogram is tolerated by 94 per cent of the rabbits. These workers further established that various lots of sulfanilamide, prepared in their laboratory, were of uniformly low toxicity. Rosenthal's experiments (1937) show comparable results. When sulfanilamide is administered to mice in doses of 1 gm. per kilogram *twice* a day for two days, followed by 0.5 gm. per kilogram *twice* a day for three days, no symptoms are produced. When the dosage is increased by 50 per cent over similar periods, weight loss occurs, but no deaths. With increase to 2 gm. per kilogram during the first period and 1 gm. during the second, a mortality of 50 per cent is produced.

There has been no mention made so far of any particular disadvantages in the use of sulfanilamide. It is becoming increasingly evident that methemoglobinemia and sulfhemoglobinemia may be complications of its use in treatment (Discombe, 1937; Paton and Eaton, 1937; Frost, 1937). Colebrook and his associates (1936) had previously reported three cases of sulfhemoglobinemia which occurred in a series of thirty-eight cases of puerperal infections treated with prontosil. They quote van den Bergh and Revers (1931), who stated that, in a case of sulfhemoglobinemia following the use of pyridium (an azo dye containing no sulfur), the simultaneous use of magnesium sulfate might have been a contributory factor; it was demonstrated in vitro that pyridium accelerated formation of sulfhemoglobin by hydrogen sulfide. Van den Bergh and Weiringa (1925) point out that the property of catalyzing sulfhemoglobin formation is apparently shared by a large variety of substances, the larger proportion of which are amino compounds or derivatives of amino compounds. Paton and Eaton (1937) were unable to detect any appreciable acceleration of the formation of sulfhemoglobin by the simple method used, on the addition of sulfanilamide to a mixture of oxyhemoglobin and hydrogen sulfide; the effects of pyridium were confirmed, however. These workers record four patients with sulfhemoglobinemia (identified by means of a microspectroscope), of whom three had had sulfates before admission. Four patients who had received no sulfate developed methemoglobinemia. The detection of sulfhemoglobin was possible more than six weeks after cessation of sulfanilamide therapy, but methemoglobin disappeared within twenty-four hours. The cyanosis is similarly persistent.

In an excellent discussion of the mechanism of formation of these abnormal pigments Paton and Eaton call attention to the work of Harrop and Waterfield (1930), who found that, while various aromatic organic compounds produce methemoglobinemia, if these substances are

given along with sulfur, the result is sulfhemoglobinemia. Paton and Eaton suggest that methemoglobin is the true toxic result of a large dose of sulfanilamide or possibly of quite a moderate dose in an unusually susceptible person; formation of sulfhemoglobin takes place only when sulfur compounds are available.

It would appear that the most severe limitation on the dosage of patients with sulfanilamide consists in its tendency to convert hemoglobin into forms useless in the transport of oxygen. It may readily be appreciated that a severe limitation should be placed on the use of sulfates or other sulfur-containing drugs before or during sulfanilamide therapy. Doubtless the spectroscope will prove to be of the greatest aid in the detection of poisoning by sulfanilamide and related drugs and will be a more delicate test than the clinical observation of cyanosis.

A further note of caution should be sounded as regards the possibility of the production of acidosis. Southworth (1937) reports the occurrence of a variable but consistent drop in the carbon dioxide combining power of the blood plasma, sometimes without clinical evidence of acidosis. Further, it has been reported, as might be expected, that this drug is capable of producing agranulocytosis.

It is evident that the clinician has at his disposal a new drug, with undoubted value in the treatment of many infectious conditions of a hitherto most refractory nature. As is nearly always the case in the use of chemotherapeutic agents, this drug is not without action upon the host, and the disadvantages should be appreciated and emphasized in order to dampen somewhat the not surprising enthusiasm which has followed the introduction of this new approach toward a "*Therapia Magna Sterilisans*," hoped for years ago by Ehrlich.

In conclusion a plea is made for the general use of the term *Sulfanilamide*, approved by the Council on Pharmacy and Chemistry of the American Medical Association, in preference to the numerous trademarked names, some of which are already in common usage.

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RESULTS OF SULFANILAMIDE TREATMENT AT THE BABIES HOSPITAL, NEW YORK CITY

A Survey of 58 Cases Observed Prior to June 10, 1937

Rustin McIntosh, M.D., Daniel A. Wilcox, M.D., and
F. Howell Wright, M.D.
New York, N. Y.

IN THE accompanying table, which summarizes a portion of the experience with sulfanilamide at the Babies Hospital in New York, only those cases are included in which the drug was given what might be considered a fair trial. A number of cases have been excluded from the survey because treatment was carried out over too short a time or in too haphazard a fashion to warrant any reasonable evaluation of the result. The method of scoring is open to criticism since it rests partly on an *ex post facto* judgment of the record; but in all instances the effort has been conscientiously made to put the burden of proof on the agent being studied.

We have applied the rating "favorable" to those cases in which the patient receiving sulfanilamide appeared to do better after the institution of this therapy than we should have expected him to do otherwise. This is obviously a personal judgment and consequently admits of a divergent interpretation. The rating "questionable" has been applied to those cases in which the patient's course did not seem to us to have been clearly influenced, whether his course was for better or for worse. Thus, we have characterized as "questionable" the results in all of the cases of otitis media caused by hemolytic streptococcus, in spite of the fact that the patients all made satisfactory recoveries, for the reason that with the knowledge available in a given instance the course of the disease could not have been predicted. On the other hand, in the conditions in which the outcome was expected to be fatal and in which no influence of sulfanilamide could be clearly made out one way or the other, the designation "questionable" has again been used.

It was our intent to reserve the term "unfavorable" for cases in which sulfanilamide evidently did harm; no cases fell into this category. We had one patient who was nauseated by the drug (though he later tolerated it perfectly well), another in whom sulfanilamide was suspected of causing fever, and a third in whom granulocytopenia developed during the course of an infection while small doses of sulfanilamide were being given; these, like the familiar cyanosis, were all minor detractions which had no clear influence on the main condition in hand, and have been disregarded in the tabulation.

Among the various hemolytic streptococcal infections, the results appear to be especially clear-cut in erysipelas, bacteriemia, and so-called primary peritonitis. In these groups there was comparatively little clouding of the issue by a complicated therapeutic program; aside from the administration of sulfanilamide and, in a few cases, of prontosil, therapy was mainly symptomatic and supportive, and in no instance was any other *ad hoc* measure, such as antistreptococcal serum, applied. The unfavorable outcome which one expects in patients as young as ours on the basis of past experience contrasts sharply with the good results obtained. With mastoiditis the results likewise seem to be encouraging, although here the judgment is admittedly more difficult.

Our patients with meningococcus meningitis both received antiserum and sulfanilamide together, making strict evaluation impossible. On the basis of the patients' ages we have scored one case "favorable," the other "questionable."

TABLE I

RESULTS OF TREATMENT WITH SULFANILAMIDE
BABIES HOSPITAL, NEW YORK

	FAVORABLE	QUESTIONABLE	UNFAVORABLE	TOTAL CASES	
Hemolytic streptococcus infections					
Pharyngitis and tonsillitis	2	3	0	5	
Peritonsillar abscess	0	1	0	1	
Adenitis, nonsuppurative	1	1	0	2	
Adenitis, suppurative	0	2	0	2	
Otitis media	0	6	0	6	
Mastoiditis	5	7	0	12	
Maxillary sinusitis	1	1	0	2	
Ethmoidal sinusitis	1	0	0	1	
Laryngotracheitis	0	1	0	1	
Pneumonia	1	0	0	1	
Peritonitis, "primary"	2	1	0	3	
Bacteriemia	2	0	0	2	
Erysipelas	7	1	0	8	
Scarlet fever	0	1	0	1	
Skin infections, other than erysipelas	2	0	0	2	
	24	25	0		49
Pneumococcus Type III infections					
Otitis media	1	1	0	2	
Pneumonia; empyema	0	1	0	1	
	1	2	0		3
H. influenzae infections					
Laryngotracheitis	0	1	0	1	
Meningitis	0	2	0	2	
	0	3	0		3
Meningococcus infections					
Meningitis with bacteriemia	1	1	0	2	
					2
Miscellaneous conditions					
Lymphatic leucemia	0	1	0	1	
					1
Total cases in this report					58

A few patients received injections of prontosil either in place of sulfanilamide or, more often, in conjunction with it. From such meager numbers it would be impossible to evaluate these results separately. It is our impression that the addition of prontosil conferred no particular advantage.

We have done little experimenting with dosage, methods of administration, and other variables. The few determinations of the level of sulfanilamide in the blood and the quantity of methemoglobin formed, mentioned in the case abstracts but not summarized separately, comprise part of a study which is soon to be reported by Lockwood and other associates. It is only too evident that nothing more than a preliminary survey of the merits and limitations of sulfanilamide has been thus far accomplished; it is equally evident that further study is warranted.

Table I summarizes the data, and the case abstracts follow.

CASE ABSTRACTS

Hemolytic Streptococcus Infections

Acute Pharyngitis and Tonsillitis

Case 1.—J. S. (No. 518065), female, aged two years, had had an upper respiratory infection with fever for about two weeks before admission. She showed pharyngitis and clinical picture of maxillary sinusitis, not confirmed by roentgenogram. Throat culture showed a moderate number of colonies of *Streptococcus hemolyticus*, though *Staphylococcus albus* predominated. Blood culture was sterile. Sulfanilamide was commenced by mouth two days after admission at dosage of 1.8 gm. per day. The temperature reached normal on the day on which sulfanilamide treatment was begun and remained so. Result: questionable.

Case 2.—M. W. (No. 463128), female, aged ten and a half years, was admitted after having shown signs of Sydenham's chorea for one month at home. Fever therapy and sedatives were tried without much effect on the choreic symptoms. Toward the end of her fourth week in hospital she developed acute pharyngitis with fever of 104° F. and *Streptococcus hemolyticus* predominating in throat culture. Sulfanilamide commenced by mouth at dosage of 3 gm. per day for three days, 1.8 gm. per day for one day, then 1.5 gm. per day for five days. Blood content of 28 gamma sulfanilamide per cubic centimeter reached two days after starting sulfanilamide; methemoglobin was 7 per cent. The fever accompanying the pharyngitis subsided at about the rate one would expect with no therapy, remaining just above the normal level for about five days and then showing a secondary rise about ten days after the initial rise. The erythrocyte sedimentation rate remained at a moderately elevated level and electrocardiogram showed changes indicative of myocardial damage which had not been present before. She was discharged at the end of seven weeks in hospital with considerable improvement in chorea but with more of a threat of rheumatic carditis. Result: questionable.

Case 3.—W. O'R. (No. 496607), male, aged six years, developed a severe sore throat with high fever, chills, and delirium three days before admission. Examination showed fever of 104.6° F. and acutely inflamed, enlarged tonsils, with pure culture of *Streptococcus hemolyticus* obtained from throat. Sulfanilamide, 0.6 gm. by mouth, was given on the day after admission. The daily dose thereafter until the day of discharge, on the sixth day, was 1.8 gm. The temperature fell to normal

on the third day, the second day of therapy, and remained normal until discharge. Throat culture was not repeated after the use of sulfanilamide. The patient developed considerable cyanosis, and his methemoglobin level reached 8 per cent. Result: questionable.

CASE 4.—A. S. (No. 382278), female, aged three and a half years, had had an irregular fever with cough and anorexia for ten days and earache for three days before admission. Physical examination showed left catarrhal otitis media, acute tonsillitis and pharyngitis, and right-sided bronchopneumonia, with fever of 103.2° F. Throat culture grew many colonies of *Streptococcus hemolyticus*. Sulfanilamide was started on the fifth day and continued for six days, the patient receiving 2.4 gm. daily. Temperature remained below 100.2° F. after the institution of therapy, and throat culture showed no *Streptococcus hemolyticus* after the third day. The resolution of physical signs was gradual over a period of two and a half weeks. Result: favorable.

CASE 5.—M. G. (No. 289937), male, aged eight and a half years, was admitted with vomiting and abdominal pain of one and a half days' duration. He had fever of 105° F., mild pharyngitis, signs of peritonitis, and was extremely toxic, with polymorphonuclear leucocytosis. Abdominal paracentesis giving no positive information, laparotomy was performed; the appendix was normal, no peritonitis was found. Blood culture was sterile. Throat culture showed many colonies of *Streptococcus hemolyticus*, which gradually disappeared from cultures repeated during the ensuing week. Sulfanilamide was given by mouth, 2.4 gm. per day, beginning two days after admission and continuing for a week. The temperature began to subside on the day on which the drug was started, reaching normal on the following day and remaining down. Result: favorable.

Peritonsillar Abscess

CASE 6.—R. A. (No. 244452), male, aged six and three-fourths years, developed an abscess in left tonsillar fossa about one and a half years after tonsillectomy. It was incised, with release of large amount of pus from which *Streptococcus hemolyticus* was recovered in pure culture. Sulfanilamide was given in dosage of 2.4 gm. per day. No striking effect on clinical course and no subsequent bacteriologic studies. Result: questionable.

Adenitis, Nonsuppurative

CASE 7.—L. C. (No. 456185), female, aged nineteen months, had had a cold with cough for six days, drowsiness, high temperature, and refusal of food for four days. Temperature was 105° F. on admission with swelling of cervical glands and marked pharyngitis. Throat culture showed *Streptococcus hemolyticus* predominating. Sulfanilamide was given by mouth, 1.2 gm. per day for six days. Temperature dropped to normal within forty-eight hours and the swelling of the glands subsided quite rapidly, the glands being impalpable in one week. The leucocytosis of 25,000 on the day of admission dropped to 8,700 on the next day. Result: favorable.

CASE 8.—R. K. (No. 504091), male, aged four and a half years, had had pharyngitis with fever and enlarged cervical nodes for four days before admission. Throat culture showed *Streptococcus hemolyticus* predominating. Blood was culture sterile. Sulfanilamide was given by mouth, 2.4 gm. per day, on the third day in hospital, after temperature had begun to subside. Temperature continued to fall, and the nodes diminished in size. On discharge, nine days after admission, *Streptococcus hemolyticus* still predominated in throat culture and was present in nose culture. Blood level of 4 per cent methemoglobin reached, and 25 gamma of sulfanilamide per cubic centimeter of serum. Result: questionable.

Adenitis, Suppurative

CASE 9.—M. G. (No. 351352), female, aged eleven years, had a swelling in the right side of the neck which gradually increased in size and became fluctuant during the week preceding admission. The temperature was 101.6° F. on admission. An incision was made immediately, and a large amount of pus was obtained, showing *Streptococcus hemolyticus* in pure culture. Sulfanilamide, 1.2 gm. daily, was given by mouth, beginning on the day after admission and continuing until discharge, sixteen days later. The temperature, which was falling at the time sulfanilamide was started, remained normal thereafter. Result: questionable.

CASE 10.—L. M. (No. 517634), female, aged three years, was admitted because of fever and enlarged cervical lymph nodes with abscess formation. The abscess was drained on the day after admission and showed *Streptococcus hemolyticus* in pure culture. The fever subsided before sulfanilamide was started. Three days after drainage of the abscess she was given sulfanilamide by mouth, 1.8 gm. the first day, subsequently 0.9 gm. per day. For the remainder of convalescence she was afebrile. Result: questionable.

Otitis Media

CASE 11.—W. M. (No. 505162), male, aged seven years, had severe pharyngitis twelve days before admission, followed by cervical adenitis and purulent otitis media. On admission, the left ear was discharging, and *Streptococcus hemolyticus* was recovered on culture; the same organism predominated in throat culture. Sulfanilamide had been given in unknown dosage for two days preceding admission, and it was resumed at a dosage of 2.4 gm. per day 2 days after admission; the dosage was raised two and a half weeks after admission to 3.6 gm. per day and was decreased again six weeks after admission to 2.4 gm. per day, the dosage level on discharge seven weeks after admission. The patient underwent mastoidectomy two weeks after admission (culture gave no growth) and incision of abscess of cervical lymph node (no culture reported), with slow but steady improvement and defervescence. Two transfusions were given. No cyanosis was reported, but patient's hemoglobin level ranged only from 9.2 to 11.9 gm. per 100 c.c., even with transfusion. Five blood cultures gave no growth. Result: questionable.

CASE 12.—L. B. (No. 505087), female, aged four and a half years, had acute purulent otitis media following respiratory infection of influenzal type. *Streptococcus hemolyticus* was obtained in culture from each ear. Sulfanilamide was begun on third day in hospital, 1.8 gm. per day for three days, then gradually reduced in amount for the next five days. On the fourteenth day in hospital, because of a spike of fever, sulfanilamide was resumed at dosage of 1.8 gm. per day, which was tapered off much as before over a ten-day period. Cervical adenitis appeared but did not progress to abscess formation. Mastoidectomy was not required. Result: questionable.

CASE 13.—E. S. (No. 487282), male, aged five and a half years, had had purulent otitis media for ten days before admission, with persistent fever. Culture of the ear discharge taken on admission showed *Streptococcus hemolyticus* in pure culture. Sulfanilamide was given at a dosage of 2.4 gm. per day. Since temperature had been normal for nearly twenty-four hours by the time sulfanilamide was commenced, the effect of the drug is not certain. Patient made satisfactory recovery and left hospital at end of one week. Result: questionable.

CASE 14.—P. C. (No. 449818), male, aged nine and a half years, had had bilateral otorrhea for one day before admission. Culture yielded *Streptococcus hemolyticus* in pure culture in discharge from each ear. Oral administration of sulfanilamide was begun twenty-four hours after admission, with fluctuating dosage averaging

about 1.2 gm. per day. The temperature fell to normal four days after admission (three days after commencement of sulfanilamide) and remained so for six days until discharge. Result: questionable.

CASE 15.—L. C. (No. 456185), female, aged twenty-one months, was admitted with bilateral otitis media of twenty-four hours' duration. Both eardrums were incised, and the pus obtained gave pure culture of *Streptococcus hemolyticus*. Sulfanilamide was commenced by mouth the day after admission at dosage of 1.2 gm. per day. The temperature fell to normal on the day after this treatment was begun and remained so for six days, after which it began to rise again although the sulfanilamide was continued and the local process in the ears appeared to be regressing. Sulfanilamide was continued during nine more days of this unexplained fever. When administration of the drug was discontinued, the fever was somewhat milder but persisted for another one and a half weeks. Mastoiditis was suspected but could not be confirmed by roentgenogram because adequate films could not be obtained. Result: questionable.

CASE 16.—M. L. (No. 403853), female, aged six and a half years, had had swelling of the cervical lymph nodes for one week and pain in the right ear for one day. At the time of admission her temperature was 101° F. Right myringotomy yielded pus with pure culture of *Streptococcus hemolyticus*. During the next thirty-six hours the temperature remained above 102° F. Sulfanilamide, 1.2 gm. daily, was started twelve hours after admission and continued until the time of discharge, eight days later. During the last six days in hospital the temperature ranged from 98° to 100° F. Result: questionable.

Mastoiditis

CASE 17.—B. M. (No. 341699), female, aged eight and a half years, had had otitis media requiring paracentesis of right drum ten days before admission. Because of persistence of fever, sulfanilamide medication was begun one and a half days before admission, 4 gm. being given by mouth in forty hours. This suppressed the fever but induced cyanosis. Culture of discharge from ear showed *Streptococcus hemolyticus*. Because of aggravation of local condition, right mastoidectomy was performed four days after admission, and sulfanilamide therapy was resumed one day after operation at dosage of 3.6 gm. for the first day, 1.8 gm. for the second day and 1.5 gm. a day thereafter for three days, when it was stopped for recurring cyanosis. The temperature gradually returned to normal. Administration of sulfanilamide was thought to induce nausea in this patient; its effect on the course of the infection was not definite. Result: questionable.

CASE 18.—P. B. (No. 505094), male, aged five and a half years, was admitted to the hospital with pneumonia (pneumococcus Type III) and bilateral otitis media (pneumococcus Type III). Throat culture showed pneumococcus and *Streptococcus hemolyticus* in about equal numbers; blood culture was sterile. The pneumonia responded well to intravenous administration of type-specific rabbit antipneumococcus serum, but the ear condition progressed to bilateral mastoiditis requiring mastoidectomy thirteen days after admission. Ten days after operation, culture of the discharge from the mastoid wounds, which had previously shown pneumococcus Type III in pure culture, yielded *Streptococcus hemolyticus* as predominating organism. Fourteen days after operation sulfanilamide was commenced by mouth at dosage of 0.9 gm. per day. The temperature, which had been falling at the time the drug was begun, continued to drop and reached normal and the second day of sulfanilamide treatment, where it remained for the remaining two and a half weeks of the patient's stay in hospital. Result: questionable.

CASE 19.—J. S. (No. 454782), female, aged twenty-one months, had had right-sided otorrhea for three weeks before admission. At mastoidectomy, performed four days after admission, pure culture of *Streptococcus hemolyticus* was recovered. The fever was slow in abating, and on the eleventh day after operation sulfanilamide treatment was begun at a dosage of 2.4 gm. orally per day. The temperature fell to normal within twenty-four hours of commencement of this regime and remained so during the subsequent eight days of the patient's stay until she left the hospital. Result: favorable.

CASE 20.—I. M. (No. 504376), female, aged two years, four months, had had bilateral otorrhea for one month before admission. Culture of the discharge showed *Streptococcus hemolyticus* and *Staphylococcus aureus*. Conservative treatment was attempted, but while under observation the patient developed suppurative cervical lymphadenitis (*Streptococcus hemolyticus*) requiring incision and drainage. Four weeks after admission bilateral mastoidectomy was performed, *Streptococcus hemolyticus* being obtained in pure culture from both sides. A week after operation, while the temperature was still elevated, sulfanilamide therapy was instituted at a dosage of 1.2 gm. per day orally. The temperature fell to normal within twenty-four hours of the first administration of sulfanilamide and remained so during the remaining week of her stay in hospital. Result: favorable.

CASE 21.—J. G. (No. 505139), male, aged four years, had had right-sided otorrhea for ten days, and more recently signs of right mastoiditis. Mastoidectomy was performed on the day of admission; *Streptococcus hemolyticus* was obtained on culture. Blood culture showed only *B. subtilis*. Sulfanilamide therapy was commenced by mouth the day after operation at dosage of 1.8 gm. a day for two days, then 1.2 gm. a day for one day, then 0.9 gm., 0.6 gm., and 0.3 gm. on the succeeding days, after which it was stopped. Convalescence was uneventful with no fever after the first postoperative day.

He was readmitted three days after discharge with recurrence of fever; there was clinical and roentgenologic evidence of pansinusitis. Sulfanilamide medication was resumed by mouth at dosage of about 1.5 gm. for five days, then 1.2 gm. for four days, then 0.9 gm. for four days. The fever subsided six days after starting this second course of sulfanilamide. Result: questionable.

CASE 22.—S. B. (No. 516001), female, aged two years, had had bilateral otorrhea for a week before admission. During the first two weeks in hospital her fever subsided gradually, but local signs of mastoiditis developed and were confirmed by roentgenogram. Bilateral mastoidectomy was performed two weeks after admission; *Streptococcus hemolyticus* in pure culture was recovered from both sides. Temperature rose again after operation, and the chart showed spikes for a week. Six days after operation, sulfanilamide was begun by mouth at dosage of 1.8 gm. per day. The temperature returned to normal on the second day of sulfanilamide treatment and remained normal until discharge two and a half weeks after mastoidectomy. Result: favorable.

CASE 23.—A. L. (No. 505161), female, aged six years, had had lobar pneumonia (pneumococcus Type III) and bilateral otitis media (pneumococcus Type III) on her first admission and had made a satisfactory recovery except for persistence of left-sided otorrhea. She was readmitted two days after discharge from her first admission, because of development of signs of mastoiditis. Mastoidectomy, performed on the day of her second admission, showed pure culture of *Streptococcus hemolyticus* in left mastoid antrum. Sulfanilamide therapy by mouth was begun on the day following operation at dosage of 1.5 gm. a day for four days, then 1.2 gm. a day for three days, after which it was stopped. Her temperature returned to normal three days after operation and remained so. Result: favorable.

CASE 24.—C. S. (No. 510478), male, aged four and a half years, had had earache for three weeks and was admitted with right otitis media and a large abscess under the galea aponeurotica in the right parietal and temporal region. At mastoidectomy there was evidence of an old mastoiditis, and on further extension of the exploratory incision a large epidural and subgaleal abscess was encountered, from which pure culture of *Streptococcus hemolyticus* was obtained. Fragments of the squamous portion of the temporal bone and of the right parietal bone showed osteomyelitis on histologic section. The blood culture was sterile. There was little constitutional disturbance, though mildly fluctuating fever persisted for five weeks. Two small transfusions were given. Sulfanilamide was commenced by mouth two days after operation at dosage of 1.2 gm. per day for two days, then 2.4 gm. per day for twenty-two days. No distinct effect of the drug on the temperature curve. Patient was discharged improved at the end of six weeks.

The patient was readmitted eleven days after discharge because of recurrence of fever and development of a convulsion. Blood culture was sterile. Right cerebral hemisphere was explored for abscess but none found; a few fragments of necrotic bone were removed from margins of the old wound of exploration and drainage. Sulfanilamide was given by mouth on the day after admission (the day of second operation) at dosage of 2.4 gm. per day for two and a half weeks, then 1.8 gm. per day for one and a half weeks. There was no fever after the day on which the second operation was performed. No cultures were taken on this admission, except the blood culture mentioned above. Convalescence was uneventful. Result: questionable.

CASE 25.—E. S. (No. 466504), male, aged twenty months, was admitted after five weeks of right-sided otorrhea with clinical signs of mastoiditis. Mastoidectomy was performed the day after admission; *Streptococcus hemolyticus* was obtained in pure culture from discharge. Mild fever occurred during the first eleven days in hospital. On the twelfth day (ten days after operation) the temperature rose to 104° F., and the tissues around mastoid wound looked red and infiltrated. Sulfanilamide was then started by mouth at dosage of 2.4 gm. per day. The temperature returned to normal in three days, with great improvement in the appearance of the wound and subsidence of congestion. A few days later an abscess behind the mastoid wound was drained. Further convalescence was uneventful. Result: favorable.

CASE 26.—R. W. (No. 505197), male, aged five and a half years, had had right-sided otorrhea for two weeks and hematuria for three days. Culture of discharge from the ear showed *Streptococcus hemolyticus*. Mastoidectomy was performed four days after admission; *Streptococcus hemolyticus* was found on culture. After operation the temperature rose, and patient became stuporous and showed nystagmus. Spinal fluid, though sterile, contained 340 cells, 60 per cent polymorphonuclears. Blood culture was sterile. Revision of the mastoid wound ten days after operation, with exposure of dura, showed no evidence of extension of the infection into the brain. Defervescence and clinical improvement progressed rapidly from this time on, the temperature reaching normal two and a half weeks after admission and remaining so throughout. Evidences of nephritis advanced during the first one and a half weeks of patient's stay in hospital, but thereafter regressed steadily. Sulfanilamide was at first poorly tolerated by mouth, and 20 c.c. prontosil (Winthrop) were given intramuscularly on the ninth, tenth, and eleventh days after admission. On the day of the second operation, two weeks after admission, sulfanilamide was begun by mouth at dosage of 3.6 gm. per day and continued for twelve days, producing 4 per cent methemoglobin in the blood and a blood level of 13 gamma sulfanilamide per cubic centimeter. Result: questionable.

CASE 27.—E. W. (No. 377486), female, aged seven and a half years, was admitted because of earache for two days. The patient had had bilateral mastoidectomy three years before, cultures at that time showing *Streptococcus hemolyticus*. At the present admission she had a postauricular abscess, with fever of 101° F. Incision and drainage were performed on the second day, and considerable pus was obtained which cultured *Streptococcus hemolyticus*. The temperature fell to 100° F., where it remained until the time of discharge. Sulfanilamide was started twelve hours after admission and continued for two and a half days, a total of 4.8 gm. being given. It was started again two days before the patient left the hospital and continued at home for three weeks. At this time she had a slight recurrence of the infection behind the ear and was readmitted for a short time. Culture at this time still showed *Streptococcus hemolyticus*. Two weeks later her temperature was normal and the ear dry. Result: questionable.

CASE 28.—P. H. (No. 505101), male, aged ten years, developed an acute otitis media two weeks before admission. The right drum was opened, pus obtained, and *Streptococcus hemolyticus* cultivated. Sulfanilamide in doses of 1 gm. per day, started twelve days before admission, was continued but failed to bring temperature to normal or to stop aural discharge. Examination on admission showed profuse, thick discharge from the right ear, but no mastoid swelling or tenderness. Sulfanilamide was increased to 2.4 gm. a day, but the child ran a spiking fever. After four days mastoidectomy was performed, and sulfanilamide was discontinued. The patient made an uneventful recovery from the operation. Repeated cultures of the aural discharge after admission to the hospital showed hemolytic streptococci with a microaerophilic tendency, growing poorly in aerobic media. Result: questionable.

Maxillary Sinusitis

CASE 29.—D. A. (No. 393043), male, aged nine years, had had maxillary and ethmoid sinusitis for six months. Nose and throat cultures showed *Streptococcus hemolyticus* as the predominating organism, and cultures from both maxillary antrums showed *Streptococcus hemolyticus* in pure culture. Under general anesthesia, permanent openings were made in both maxillary antrums, through which the antrums were subsequently irrigated. Six days after operation sulfanilamide was commenced: 1.8 gm. for one day, then 2.4 gm. a day for five days. No effect on nose and throat cultures was noted. Patient was receiving vaccine therapy at the time this was written. Result: questionable.

CASE 30.—K. H. (No. 508287), male, aged four and a half years, was admitted for chronic or recurrent pneumonia following whooping cough fourteen weeks previously. Clinical and roentgenologic signs of bilateral maxillary sinusitis were found; *Streptococcus hemolyticus* predominated in the sputum culture. During five weeks of conservative treatment, directed mainly at the sinusitis, he ran an irregular fever, and the chest showed a migrating pneumonia. Bronchoscopy was not performed. Sulfanilamide was begun by mouth at end of fifth week in hospital at a dosage of 2.4 gm. per day and kept up for two weeks, during which time he had no recurrence of fever and gained a considerable amount of weight. The lung signs cleared considerably, and he was sent home improved. Result: favorable.

Ethmoidal Sinusitis

CASE 31.—D. K. (No. 514889), male, aged six and a half years, developed right orbital cellulitis after two days of nasal discharge. Roentgenograms showed bilateral ethmoid sinusitis and probably sphenoidal sinusitis. A subperiosteal abscess was found just above right lacrimal gland; pure culture of *Streptococcus hemolyticus* was obtained. Nose culture showed the same organism. Blood cultures were sterile on three occasions. Intramuscular injections of prontosil (Winthrop) were begun

on the day of operation and were continued for five days at dosage of 30, 15, 25, 15, and 20 c.c. Sulfanilamide was given orally, beginning the day following operation, at a daily dosage of 1.8, 0.6, 1.8, 1.2 gm., then 3.6 gm. a day for five days, and then 2.4 gm. a day for two and a half weeks. Temperature, which had been 106.8° F. on day of operation, fell within five days to normal and remained so. Result: favorable.

Laryngotracheitis

CASE 32.—J. O'H. (No. 480346), male, aged fourteen months, was admitted with history of a cold for one week, fever for three days, and labored respirations for two days with a crow for the preceding nine hours. The temperature was 103° F. on admission, and there were marked retraction of chest, swelling of neck and edema, and inflammation of pharyngeal tissues. At laryngoscopy the patient suddenly stopped breathing, necessitating passage of bronchoscope and emergency tracheotomy. Cultures of pharynx and blood grew *Streptococcus hemolyticus*. He was given 1.2 gm. of sulfanilamide by mouth and 5 c.c. of prontosil (Winthrop) intramuscularly on the first day, and 0.9 gm. sulfanilamide by mouth, 2 gm. by hypodermoclysis, and 15 c.c. prontosil on second day. Only slight drop in temperature resulted; there was no clinical improvement; the patient died on the third day. The color was cyanotic from admission to death. Result: questionable.

Pneumonia

CASE 33.—S. R. (No. 517501), female, aged twenty-one months, was admitted with pneumonia, symptoms of respiratory infections having been present for ten days. Pure culture of *Streptococcus hemolyticus* was obtained by lung puncture on the day of admission. Blood culture was sterile. In the course of a week she developed a small pleural effusion, which was tapped on five occasions because of respiratory difficulty and because roentgenograms suggested that there was a large amount of fluid present, but each time only 10 to 50 c.c. of thin, straw-colored fluid were obtained, sterile on culture. Sulfanilamide was begun by mouth on the day after admission at a dosage of 2.4 gm. per day and was kept at this level for thirteen days, then 1.8 gm. per day for eight days. Pleural fluid removed one week after institution of sulfanilamide therapy contained 10 gamma sulfanilamide per cubic centimeter. The temperature curve, which reached 107° F. on the day of admission, fell gradually during the first week, rose again to 104.6° F. in the middle of the second week, and was at a normal level during the third, fourth, and fifth weeks. The patient was discharged at beginning of sixth week. She did not develop classical empyema and had no other complications. Result: favorable.

Peritonitis, "Primary"

CASE 34.—F. S. (No. 510716), male, aged twenty-two months, was admitted after three days of fever, vomiting, and diarrhea. Because of the absence of clear-cut signs of peritonitis, he was kept under observation for the first forty-eight hours in hospital, at the end of which time laparotomy was performed because of increasing abdominal tenderness and distention, rising leucocytosis, and spiking fever. Fibrinopurulent peritonitis was found, with odorless pus and pure culture of *Streptococcus hemolyticus*. The appendix, which was removed, showed only periappendicitis. Immediately following operation, sulfanilamide was started by mouth at a dosage of 1.8 gm. a day, and he was given daily intramuscular injections of prontosil (Winthrop), 20 c.c. After six days of this treatment the blood level of sulfanilamide was 38 gamma per cubic centimeter of serum, and there was less than 2 per cent of methemoglobin. Repeated blood cultures failed to show streptococci. The patient died on the twelfth day in hospital. Result: questionable.

CASE 35.—M. K. (No. 508687), female, aged eleven months, was admitted with fever, vomiting, and diarrhea of two days' duration. Blood culture showed *Streptococcus hemolyticus*. Abdominal paracentesis yielded purulent exudate with pure culture of *Streptococcus hemolyticus*. Continuous intravenous infusion was set up the day after admission and was continued for seven days, and frequent small transfusions were given (nine in all). Her course was exceedingly stormy. During the first week her temperature stayed close to 103° F.; in the second week it fluctuated more, but the peaks were higher; in the third and fourth weeks the fever abated gradually, disappearing by the middle of the fifth week. In the seventh week the patient developed a partial intestinal obstruction, without fever, requiring continuous intravenous infusion over a second period of eight days, after which the obstruction was relieved without operative intervention and the patient went on to recovery, leaving the hospital eleven and a half weeks after admission. Her blood culture showed *Streptococcus hemolyticus* on the first, second, and third days in hospital, then no growth for several days until the ninth day after admission, when *Streptococcus hemolyticus* was again recovered. The peak of her blood stream infection was reached ten days after admission, when culture showed 1,330 colonies per cubic centimeter of blood. The last positive blood culture was obtained on the twenty-second day after admission. During her second week she developed jaundice with great enlargement of the liver and serum bilirubin of 4.17 mg. per 100 c.c. Other complications which she weathered were otitis media (*Staphylococcus aureus*), infection of transfusion wound (*Streptococcus hemolyticus*) and an abscess of the soft parts of the leg a few centimeters above the transfusion wound (*Streptococcus hemolyticus*). Sulfanilamide was begun by mouth on the day after admission at a dosage of 1.8 gm. per day for two days, then 0.9 gm. per day for six days, then 0.6 gm. per day for three days; with reappearance of a positive blood culture the dose was increased to 1.2 gm. per day for four weeks, after which it was dropped to 0.9 gm. per day for four days, then 0.6 gm. per day for two days; none was given during the last five weeks of the patient's stay in hospital. Prontosil (Winthrop) intramuscularly was begun five days after admission at 20 c.c. per day and kept at this dosage for five days, then decreased gradually over the next three days, then resumed at 20 c.c. per day for twenty-five days, then 15 c.c. for four days, then 10 c.c. for two days, and then stopped. Result: favorable.

CASE 36.—L. J. (No. 517511), male, aged one year, was admitted after two days of fever and vomiting. Abdominal paracentesis yielded purulent fluid with pure culture of *Streptococcus hemolyticus*. Blood culture was sterile on several occasions. *Streptococcus hemolyticus* predominated in the throat culture. He was put on continuous intravenous infusion with no fluids by mouth for the first three days, after which oral administration was gradually resumed. Sulfanilamide was begun by mouth on the day of admission at dosage of 2.4 gm. per day; after eight days, the dose was reduced to 1.8 gm. per day for the next nineteen days, then 1.2 gm. a day for two days. Prontosil (Winthrop) was given intramuscularly, 15 c.c. a day, for fifteen days. Eight days after admission the blood showed 10 per cent methemoglobin and 17 gamma sulfanilamide per cubic centimeter. Four small transfusions were given. Recovery was uncomplicated: the temperature was normal at end of second week. Result: favorable.

Bacteriemia

CASE 37.—H. E. (No. 517552), female, aged eleven months, had had daily fever of 104° F. or more for a week, associated with an only moderately severe pharyngitis. On admission she presented the clinical picture of septicemia. Predominating organism in throat culture was *Streptococcus hemolyticus*, and the same organism was obtained in pure culture from the blood stream. A week after admission the left

eardrum ruptured spontaneously, and *Streptococcus hemolyticus* was cultivated from the discharge in pure culture. Sulfanilamide, 1.8 gm. per day, was given from the second day in hospital, and from the fourteenth to the twenty-seventh days in hospital a daily injection of 15 c.c. of prontosil (Winthrop) was given intramuscularly. Temperature gradually subsided to normal during hospital stay of four and a half weeks. Blood cultures were repeated once a week during the course of the fever; none was positive after the first. Two transfusions were given on the fourth and the fifth days in hospital; there was no operative treatment. Result: favorable.

CASE 38.—S. S. (No. 514492), female, aged two years, had had nephrotic anasarca for one month before admission. Attempts were made to release the edema with mercurial diuretics, thyroid substance, and other measures, with indifferent success. About a month after admission, patient contracted a pharyngitis with high fever and with *Streptococcus hemolyticus* in throat and blood stream. Sulfanilamide was given orally at dosage of 2.4 gm. per day during the rest of her stay (one month after development of bacteriemia). Transient cyanosis appeared during the first week of sulfanilamide therapy and disappeared while the dosage remained unchanged. The blood culture was positive for *Streptococcus hemolyticus* a second time, four days after the first positive culture, but subsequent ones were sterile. *Streptococcus hemolyticus* was recovered from the discharge from the wound left when tissues sloughed around a vein where salyrgan had been injected. Two days after institution of sulfanilamide therapy, blood content of sulfanilamide was 20 gamma per cubic centimeter; nine days later, with no change in dosage, the blood content was 1 to 2 gamma. An explanation for this was not found. The temperature curve sloped gradually downward as blood culture became sterile, the mild pyrexia persisting being attributed to local infection around the slough. With improvement from the infection a considerable loss of edema occurred, but there was a weight gain of one kilogram in two days when patient developed varicella from a hospital contact. Subsequent course was satisfactory, as the loss of edema was resumed with convalescence from chickenpox. Result: favorable.

See also Case 35, M. K. (No. 508687) under *Peritonitis, "Primary."*

Erysipelas

CASE 39.—E. S. (No. 456761), male, aged two years, was admitted to the hospital because of right mastoiditis with cortical perforation after five days of otorrhea at home. At mastoidectomy, three days after admission, pneumococcus Type I was recovered; blood culture was sterile. Nineteen days after operation, erysipelas developed around the mastoid wound, and the patient was given sulfanilamide orally, 2.4 gm. per day. Fever diminished immediately, and the temperature subsided to normal on fourth day of treatment. Spread of erysipelas was checked within one day of institution of sulfanilamide treatment. No culture was made after appearance of erysipelas. Result: favorable.

CASE 40.—K. MacG. (No. 501180), female, aged five and a half months, had had right otorrhea (pneumococcus Type VIII) for two weeks before admission. She was admitted twelve hours after onset of fever and appearance of a red spot in front of the right ear. The temperature was 103.6° F., with definite erysipelas about the draining right ear, and right cervical adenitis. Cultures from the pharynx and from the aural discharge showed *Streptococcus hemolyticus*. Sulfanilamide was given by mouth, 1.8 gm. per day for eight days. Her temperature dropped temporarily after onset of therapy, reaching normal in four days. The lesion spread for one day, then slowly faded and peeled on the sixth day. The aural discharge ceased six days after the start of the treatment. Reaction to drug:

moderate cyanosis, poor appetite, leucocytosis of 56,000 after four days. Sulfanilamide was continued, and cyanotic tinge persisted for two weeks after discharge. Result: favorable.

CASE 41.—P. H. (No. 456996), male, aged two years, was admitted with bilateral otorrhea of three weeks' duration, sagging right canal wall, and thick discharge. Culture showed *Streptococcus hemolyticus*. Nine days following right simple mastoidectomy, patient developed erysipelas in the wound. Sulfanilamide was given by mouth, 2.4 gm. per day for three days, with immediate drop in temperature from 104° F. to normal and a rapid clearing of erysipelas. Result: favorable.

CASE 42.—E. G. (No. 508710), male, aged fourteen months, was admitted with questionable erysipelas of the face. He had been exposed to the sun on the day before admission and developed erythema of both cheeks, more pronounced on the right, with fever of 104° F. Lesion was not sharply demarcated, and no streptococci could be recovered from the throat, but hematuria was present. After administration of 1.8 gm. of sulfanilamide, the temperature dropped to normal. It rose again to 103° F. two days later and remained irregularly elevated until 1.2 gm. of sulfanilamide was given daily, after which it dropped to normal and stayed there. This case is difficult to interpret, as diagnosis of erysipelas was not very clear cut. Leucocyte counts were 25,000 and 17,000 on two occasions. Result: questionable.

CASE 43.—P. W. (No. 522018), female, aged four months, was admitted with a five-day history of a spreading erythematous lesion on right thigh and labia, associated with fever. Temperature was 102° F. on admission, with definite large area of erysipelas on right thigh. She was given sulfanilamide, 1.8 gm. per day, with prompt drop in temperature to normal and rapid fading of the lesion. Result: favorable.

CASE 44.—N. O'D. (No. 465163), female, aged two years, after having a cold for one week, developed redness and swelling of the right ear 24 hours before admission, with spreading of the erythema over the face. The temperature was 104.2° F. on admission, with draining right ear and red, swollen auricle, and erythema extending over the face for a distance of about 3 cm. *Staphylococcus citreus* was cultivated from aural discharge; *Streptococcus hemolyticus*, from the throat. Sulfanilamide was given by mouth, 1.2 gm. the first day and 2.4 gm. each of the next six days. Temperature dropped promptly to normal, and the lesion faded quickly. After two days of treatment, no methemoglobin in blood, and 14 gamma of free sulfanilamide per cubic centimeter. Result: favorable.

CASE 45.—B. W. (No. 507049), male, aged eleven months, had had fever, vomiting and enlargement of cervical glands for five days. The temperature was 104° F. on admission, with pharyngitis, rhinitis, draining right ear and bulging left eardrum, and moderate enlargement of the cervical lymph nodes. Cultures from throat and from both ears following myringotomy yielded *Streptococcus hemolyticus*. No specific therapy was given, and the patient appeared to be improving until ten days after admission, when temperature rose sharply to 105° F. and an area of erysipelas appeared on the scalp. Sulfanilamide, 1.8 gm. per day, was given and temperature dropped abruptly two days later and remained there; the area of erysipelas faded; and the patient was discharged four days later to continue small doses of sulfanilamide at home. The discharge from the ears had practically stopped at the time he left hospital. Leucocytosis reached 41,000 during erysipelas. Result: favorable.

CASE 46.—R. H. (No. 515956), male, aged fourteen months, had a cold and fever for a week preceding admission. On the day of admission, a red spot appeared over

his right eye and spread rapidly. Temperature was 103° F. on admission with typical erysipelas of right eye and face, so that the eye was swollen shut, and there was some extension to the left lid. There was mild right cervical gland enlargement. *Streptococcus hemolyticus* was cultured from the throat. Sulfanilamide, 1.8 gm., was given daily, and the temperature fell, but ranged as high as 101° F. during the next week. Erysipelas did not spread but faded quite rapidly, and the child was discharged on tenth day. Result: favorable.

Scarlet Fever

CASE 47.—L. H. (No. 505073), female, aged four and one-half years, was admitted on third day of scarlet fever. Sulfanilamide was started on day of admission: 1.2 gm. a day for two days, then 1.8 gm. a day for nine days. No significant effect was noted on temperature curve, clinical course, or persistence of *Streptococcus hemolyticus* in the throat culture. The patient recovered without complications. Result: questionable.

Skin Infections
(Except Scarlet Fever and Erysipelas)

CASE 48.—J. B. (No. 487306), male, aged eight and one-fourth months, had had infantile eczema for about two and one-half months. *Streptococcus hemolyticus* was recovered from pustule in eczematous area. Sulfanilamide was given by mouth, 1.8 gm. a day for five days. There were rapid drying of the skin lesions (with no coincident local therapy) and disappearance of *Streptococcus hemolyticus* from cultures. Eosinophilia persisted, and the patient's eczema later reappeared, though *Streptococcus hemolyticus* was not subsequently cultivated from vesicle fluid. Result: favorable.

CASE 49.—B. M. (No. 513894), male, aged seven and one-half years, had had erythema multiforme bullosum for eight months. Culture from a large bulla yielded *Streptococcus hemolyticus* in pure culture. Sulfanilamide, 0.9 gm. per day, was given by mouth for two days, then 2.4 gm. per day for three days. Locally, an ointment of 5 per cent sulfanilamide in lanolin was used. The lesions healed completely in five days. No fever, leucocytosis, or elevation of erythrocyte sedimentation rate was noted during the period of observation. Comparable skin lesions recurred one month later. Result: favorable.

PNEUMOCOCCUS TYPE III INFECTIONS

Otitis Media

CASE 50.—A. E. (No. 507266), male, aged five months, was admitted because of high fever for twenty-four hours. Physical examination showed bilateral otitis media and consolidation of the left lower lobe. The temperature remained about 103° F. for the first thirty-six hours, at which time myringotomy yielded pus (pneumococcus Type III). After this, a swinging type of fever remained until the seventh day, when the temperature fell by crisis and remained normal until discharge eight days later. Sulfanilamide was given daily by clysis for four days, beginning on the day after myringotomy, in doses of 0.5 to 2 gm. After this it was given by mouth, 0.9 gm. daily. Cultures of the aural discharge, taken five days after the institution of sulfanilamide therapy, still showed pneumococcus Type III. Lung puncture at the site of consolidation revealed pneumococcus Type VII, of which a few colonies had been found in throat culture. The level of sulfanilamide in the blood reached 18 gamma per cubic centimeter after the administration of 2.5 gm. by clysis; no methemoglobin was found. Result: questionable.

CASE 51.—J. B. (No. 508288), female, aged three years, had had fever and earache for one week. On admission, both eardrums were red and bulging and were incised (pneumococcus Type III). The temperature, which was 105.6° F. on admission, remained septic in type for four days in spite of myringotomy. Sulfanilamide, 1.2 gm. daily, was started on the fourth day, three days after operation, and continued for three weeks. On the day after it was started, the temperature dropped to 99° F. and, except for one rise to 103° F. on the next day, remained normal until the time of discharge, one month after admission. Cultures taken from the ears showed only a few colonies of pneumococcus Type III on the third day after sulfanilamide was started, and they were negative one week later. Result: favorable.

Pneumonia; Empyema

CASE 52.—B. P. (No. 506538), female, aged six years, had had fever and difficult respirations for one week. On admission she showed signs of consolidation and fluid in the left chest. She was acutely ill, with considerable cyanosis, and required oxygen for the first week in addition to repeated pleural taps. Culture of the pleural fluid grew pneumococcus Type III. Sulfanilamide was started on the day after admission, 1.2 gm. daily, and was continued for five weeks. The temperature continued to run between 99° and 103° F. in spite of the drug until rib resection was done during the third week, after which it gradually fell to a normal level. Cultures of the pleural fluid showed pneumococcus Type III one week after admission, five days after sulfanilamide had been started. No methemoglobin was demonstrated in the blood. Result: questionable.

H. INFLUENZAE INFECTIONS

Laryngotracheitis, Due to H. Influenzae

CASE 53.—F. O'B. (No. 352400), male, aged four years, was admitted with a twelve-hour history of advancing laryngeal obstruction. Emergency tracheotomy was performed. Throat and two blood cultures (second and fourth days) grew *H. influenzae*. Sulfanilamide, 1.8 gm. a day, was given by mouth for first three days. The temperature, 105° F. on admission, dropped to 100° F. on third day and stayed there. Second positive blood culture was obtained on day that drug was discontinued. Result: questionable.

Influenzal Meningitis

CASE 54.—D. B. (No. 241631), male, aged six years, was admitted with a twelve-hour history of drowsiness and stiff neck. *H. influenzae* was found on smear and culture of spinal fluid. Anti-influenza serum was given intravenously and intrathecally twice daily without effect. Sulfanilamide, 1.8 gm. per day, was also given for a period of ten days with no apparent benefit. The child died nineteen days after admission. Result: questionable.

CASE 55.—B. Z. (No. 517508), aged six years, was admitted because of pain in the ears, fever, headache and vomiting for three days. Culture after myringotomy at the time of admission showed *Streptococcus hemolyticus* to be the predominating organism. Blood culture, taken two days later, grew *H. influenzae*. At mastoidectomy, one week after admission, *Streptococcus hemolyticus* was again recovered. The temperature had been of a septic type since admission and continued so after operation. Signs of meningitis soon appeared, and the spinal fluid grew *H. influenzae*. Intravenous and intrathecal anti-influenza serum was given with only temporary benefit. Sulfanilamide was started one week after operation, 3.6 gm. daily, but had no effect on the growth of either *Streptococcus hemolyticus* or *H. influenzae*. Patient died one month after admission. Result: questionable.

Meningococcus Infections

Meningitis With Bacteriemia

Case 56.—R. P. (No. 505419), male, aged five months, was admitted within twenty-four hours of onset of symptoms of meningitis. Lumbar puncture, performed on admission, showed organisms with characteristic morphology of meningococcus. Patient was given antimeningococcus serum intrathecally and a hypodermoclysis of Ringer's solution containing 1 gm. of sulfanilamide. The same combination was administered twelve hours later, and again twenty-four hours after the second dose. The first sample of spinal fluid contained viable meningococci of Type II; no growth was obtained from succeeding fluid specimens. Admission blood culture contained meningococci; a second blood culture, made on the second day in the hospital, showed no growth. The patient made a rapid and complete recovery without further therapy. Result: favorable.

Case 57.—F. S. (No. 516136), female, aged four and three-fourths years, was admitted after twenty-four hours of symptoms of meningitis. Lumbar puncture showed characteristic findings of meningococcus meningitis, with organisms on smear and culture, and blood culture on admission was positive for meningococcus Type I. On the evening of admission 30 c.c. of antimeningococcus serum was given intrathecally, and a hypodermoclysis of 200 c.c. of 1 per cent solution of sulfanilamide was given. Serum was given intraspinally on each of the next two days. Clysis of 2 gm. sulfanilamide was repeated on the second day in hospital. Sulfanilamide was given by mouth, 1.8 gm. on the fourth day, 2.4 gm. on the fifth day, and 0.6 gm. on the seventh day. By this time the spinal fluid cell count had dropped to 120 cells per cubic millimeter, and the blood culture was sterile; spinal fluid culture became sterile on the second day in hospital. An uncomplicated recovery followed. Result: questionable.

Miscellaneous

Lymphatic Leucemia

Case 58.—John O'C. (No. 505048), male, aged three years, was admitted with typical picture of acute lymphatic leucemia with white blood cells 46,000 per cubic millimeter, hemoglobin, 4.6 gm. per 100 c.c.; and red blood cells, 1.65 million per cubic millimeter. Sulfanilamide, 1.5 gm. per day, was given for one week with no noticeable effect. The leucocyte count had fallen to 4,450 before drug was started and did not go below 3,000. The hemoglobin level and red blood count fell in eighteen days to one-third of the values on admission. Yellow tinge of skin was observed after starting sulfanilamide, but no bilirubin determinations were made. Platelet count was consistently low and not obviously affected by the drug. Result: questionable.

REPORT ON THE USE OF SULFANILAMIDE AND ITS DERIVATIVES AT THE CHILDREN'S HOSPITAL OF CINCINNATI

A. Graeme Mitchell, M.D., and Walter H. Trachsler, M.D.
Cincinnati, Ohio

SINCE January, 1937, thirty-four patients suffering from various infections have been treated with sulfanilamide or its derivatives in the Children's Hospital of Cincinnati. Table I outlines some features of the case histories of these patients.

Table I

DISEASE	NUMBER CASES	RECOVERED	IMPROVED	UNIMPROVED	DIED	ORGANISM
Septicemia						
streptococcic	3	2			1	Hemolytic streptococcus
staphylococcic	1				1	Hemolytic *Staphylococcus aureus*
Meningitis						
streptococcic	7	4			3	Hemolytic streptococcus
meningococcus	3	3				Meningococci
pneumococcic	1	1				Pneumococcus type V
Mastoiditis	1	1				Hemolytic streptococcus
Otitis media	9	8	1			Hemolytic streptococcus
Sinusitis	1	1				Hemolytic streptococcus
Erysipelas	2	2				
Scarlet fever	1	1				Hemolytic streptococcus
Pyelitis	1		1			*Bacterium coli*
Chronic infectious arthritis	1				1	-
Endocarditis subacute bacterial	1			1		Intermediate streptococcus
Undiagnosed febrile attacks (grippe?)	2	2				-

Discussion.—It is obviously fortunate that no conclusions need be attempted from this meager experience. Some comment may be permissible. The patients treated with sulfanilamide and its derivatives as noted in Table I were selected usually because of the severity of their infection and of their general condition. No comparable control series can be cited. Furthermore, other forms of treatment were administered at the same time as sulfanilamide therapy, this combination making difficult evaluation of the curative effect of the sulfanilamide.

From the Children's Hospital, Cincinnati, the Children's Hospital Research Foundation, and the Department of Pediatrics, University of Cincinnati.

Small doses of these drugs were administered early in our experience, but soon they were increased. Usually the procedure was to inject 5 c.c. of prontosil soluble intravenously every four hours (daily amount 30 c.c.) for the first two or three days; then the same daily dose was given intramuscularly until the patient's general condition improved. At this point in the treatment, prontylin or sulfanilamide in a tablet of 0.3 gm. was administered three times a day. The dose as mentioned was that for children between six and twelve years of age, younger children receiving approximately one-half these amounts and infants one-third. Recently our inclination has been to employ the drug only by oral administration. Prontylin and prontosil were employed in most of the cases cited. Sulfanilamide was later used for oral administration in place of prontosil.

Two of the three patients with *streptococcic septicemia* recovered. The result in one of these, however, cannot reasonably be attributed to the administration of prontosil, especially since the dosage was rather small. Furthermore, the patient received antistreptococcic serum and transfusions. Death in the second patient with streptococcic septicemia could hardly be considered as a failure of sulfanilamide therapy, since, here again, the dosage was probably insufficient to insure a satisfactory level of the drug in the blood. Recovery in the third patient was probably influenced by sulfanilamide therapy. The case history of this patient is reported in detail.

CASE REPORT

A white boy, seven years of age, was admitted to the hospital on April 7, 1937. Two weeks previously he had measles. One week later he complained of earache. A right myringotomy was performed, but the left ear began to discharge spontaneously. Two days before admission the boy complained of pain in his right leg and soreness of his neck upon motion. Nausea and headache were absent. Physical examination showed an acutely ill boy with a temperature of 99° F., a pulse rate of 100, and a respiratory rate of 22. There was generalized desquamation over the body. Both ears were draining. There was no mastoid tenderness. The pharynx was reddened. The neck showed a rather diffuse, soft fullness extending to the clavicular-sternal junction. This swelling was tender upon firm palpation. Nothing abnormal was found in the physical examination of the chest. A systolic murmur was heard over the mitral area. The abdomen was not tender. The arms and the left leg showed no restriction of mobility. The right hip was almost fixed, no flexion or abduction being possible and rotation being restricted. Over the sacrum there was a decubitus, which was not ulcerated. The reflexes were normal. A spinal tap was at once performed, and the fluid was found to be clear, under normal pressure, and to contain 15 cells to the cubic millimeter. Pandy's test was negative, and the culture showed no growth. The urine was negative. The hemoglobin was 11.6 gm.; the red blood cells numbered 4,170,000; the white blood cells, 23,400. The differential count showed 80 per cent polymorphonuclear cells, 6 per cent lymphocytes, 12 per cent large mononuclear cells, and 2 per cent transitional cells. Roentgenographic examination of the mastoid regions showed haziness of the right side and to a lesser degree of the left side, but apparently no broken-down cell structure. Roentgenographic examination of the right hip showed nothing abnormal.

Immediately after admission the patient's temperature rose to 105.5° F., and there were several chills. A blood culture was taken which was positive for hemolytic streptococci. Prontosil (5 c.c. every four hours) was started immediately. The temperature remained high and was of a septic type. Several blood transfusions were given. On April 10 a right mastoidectomy was performed. One large cell at the tip of the mastoid was filled with pus. This cell was connected with the antrum by a slightly infected tract of bone. The sinus wall appeared to be intact, but on exposure of the sinus the color was gray. The sinus was opened, and a thrombus was disclosed about one inch in length. The internal jugular vein was ligated at the cricoid cartilage. After the operation the temperature was less fluctuant but still remained high (between 102 and 105° F.). On April 12 the child again had a severe chill and was cyanotic. The spinal fluid at that time was under slightly increased pressure and blood tinged, the sugar content being normal. Culture of the spinal fluid showed no growth, neither did the cultures of the pus from the right mastoid or of the thrombus from the lateral sinus. (This might be attributed to the effect of prontosil and prontylin, which had been started two days before operation and four days before the second spinal tap.) On April 14 the left mastoid was opened and a small amount of pus was found in the antrum; otherwise the mastoid was negative. The lateral sinus was then exposed over a small area and was found to be normal. The day after this operation the temperature began slowly to fall and soon ranged between 100° F. and 102° F., remaining there for several days. On April 17 the left ankle joint was swollen and tender. Otherwise the child was comfortable, and his general condition was good, although the blood culture still showed hemolytic streptococci. Another culture taken on May 5 was negative. The mastoid wound healed, but the right leg developed a flexion contracture of the hip. On May 20 an incision was made into the right hip, and the joint was drained. The pus obtained at operation was sterile. The roentgenographic examination of the pelvis showed bone destruction involving the neck and possibly the head of the right femur. After May 25 the temperature remained normal. The boy is still in the hospital on a Bradford frame. There is little drainage from the right hip at the present time, and the general condition is excellent.

The treatment in this case consisted in blood transfusions and the administration of prontylin and prontosil soluble. Five hundred seventy-five cubic centimeters of citrated blood had been given in five transfusions. Thirty-five cubic centimeters of prontosil soluble were injected intravenously and 50 c.c. intramuscularly. Up to June 22, when the drug was discontinued, a total of 228 tablets (each of 0.3 gm.) of prontylin had been given orally. The patient showed no apparent toxic symptoms from the medication.

The patient with *staphylococcus septicemia* was desperately ill on admission and had a pyoarthritis of the left ankle. He died two days after admission.

Four of our seven patients with *streptococcic meningitis* recovered. These will be the subject of a subsequent detailed report (p. 248). The recovery rate compares very favorably with that obtained in the Children's Hospital Clinic in the past ten years—only one of fourteen patients with streptococcic meningitis recovered. In the Cincinnati General Hospital, fifty-seven patients with streptococcic meningitis were admitted over a period of fourteen years and only one of these recovered (Zeligs, M: Am. J. Dis. Child. **50**: 1497, 1935). It would appear that treatment with sulfanilamide and similar drugs has a definite beneficial effect in this condition. It is not possible to decide from our experience

how effective the drug would be if employed without other therapy. All of the four patients who recovered had streptococcic meningitis of otitic origin; all had purulent mastoiditis which was surgically drained; and all but one received antistreptococcic serum. Of the three patients who died, one lived only twenty-four hours after admission; one, four days; and the third, eleven days. This last patient had a skull fracture and a green-producing streptococcus was found in the spinal fluid. Intraspinal administration of sulfanilamide was not tried in any of these cases.

In three patients with *meningococcic meningitis* a 1 per cent solution of sulfanilamide was administered intraspinally, the daily amount being from 10 to 20 c.c. In addition prontylin was given by mouth. Since antimeningococcus serum and meningococcus antitoxin were given in large amounts in these three cases, it is impossible to decide whether the sulfanilamide type of drug was in any way responsible for the cure. The spinal fluid in one of these patients had been positive for meningococci for ten days but became negative the day following the first intraspinal injection.

In the patient with *pneumococcic meningitis* prontylin was given orally, one tablet every four hours for seven days. It was then discontinued while the fever was still high and the patient's condition unimproved. Optochin had been given at the same time as prontylin and was continued subsequently. In both the spinal fluid and at the mastoid operation, type V pneumococcus was recovered. It would appear reasonable to attribute the favorable outcome to optochin rather than to prontylin.

Sinusitis, mastoiditis and *otitis media* of streptococcic origin apparently were favorably affected by sulfanilamide treatment.

Two cases of *erysipelas* in small infants appeared to respond well to prontylin administration. The fact that one child had recurrence of the cellulitis two days after the drug was stopped would seem to indicate that the therapy should be continued for a few days after fever has subsided and the local condition improved.

No curative effect of sulfanilamide was seen in a case of *subacute bacterial endocarditis*, in which an intermediate type of streptococcus was found in the blood. After this patient had had 225 c.c. of prontosil by injection and 119 prontylin tablets orally, hematuria developed, this ceasing when the medication was discontinued.

The patient with Still's disease, or *chronic infectious arthritis*, showed no improvement under prontylin therapy while he was in the hospital. Prontylin was given in larger doses by his family physician after he was discharged from the hospital, the joint symptoms coincidentally improving. Later the child was admitted with a marked agranulocytosis.

a severe anemia, and a necrotic type of stomatitis and pharyngitis. Death followed. The necropsy report at the time of this review is not available.

In addition to the agranulocytosis just mentioned and possibly to be attributed to sulfanilamide therapy, we have occasionally seen other symptoms probably resulting from the *toxic effect of the drug*. Rashes of a maculopapular, morbiliform type, and pyrexia are among these. A few children complained of a burning sensation in the stomach immediately after prontosil was given intravenously. We have not seen severe cyanosis although mild degrees have occurred which ceased shortly after discontinuation of the drug. Acidosis did not occur in our patients to our knowledge, carbon dioxide determinations being made when indicated. Nausea was seldom so marked that administration of prontylin had to be discontinued.

One of us (W. H. T.) has used sulfanilamide and its derivatives for two years in the clinic of Professor Fanconi in Zurich. Our impression from clinical observation is that this type of drug appropriately employed has value, especially in the treatment of streptococcic infections. We are planning in the future to study the quantitative aspects of the drug in the blood stream and also to make frequent determinations for methemoglobinemia.

REPORT OF CASES TREATED WITH SULFANILAMIDE (PRONTOSIL AND PRONTYLIN)

DEPARTMENT OF PEDIATRICS, UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA

IRVINE McQUARRIE, M.D.
MINNEAPOLIS, MINN.
Minneapolis General Hospital

CASE 1.—Diagnosis: (1) Acute mastoiditis, right, (2) scarlet fever, (3) encephalitis, (4) possible meningitis, and (5) bronchopneumonia (aspirational).

The history is that of a white male, aged twelve years, who during the third week postscarlet fever developed an earache and then a spontaneous rupture of the right drum twenty-four hours after the onset of pain. The morning of admission, forty-eight hours after onset of earache, he awakened with a severe headache. Three hours later he became comatose and rigid all over. At this time he was brought to the hospital.

Physical examination revealed an acutely ill boy whose entire body was extremely rigid. The throat was filled with much mucus. The chest was full of coarse râles. The right ear canal was filled with pus. No mastoid redness or swelling was present. The temperature was 104.6° F. rectally. X-ray films of chest at the bedside proved unsatisfactory. Spinal tap revealed a cloudy fluid containing 1,290 cells (90 per cent polymorphonuclears), 290 mg. of protein, and negative smears and cultures.

Five cubic centimeters of *prontosil* was started and given daily, every four or five hours, for a total of 27 injections. A right mastoidectomy was done on the second day. Culture of the pus showed hemolytic streptococci. Spinal puncture on the third day revealed normal fluid. The patient remained in coma until death, the body quite rigid. The temperature remained around 103 to 104° F., and the chest was still full of coarse and fine râles.

Postmortem examination showed normal meninges, hemorrhagic encephalitis, and bronchopneumonia.

CASE 2.—Diagnosis: (1) Recurrent rheumatic arthritis and carditis, (2) subacute bacterial endocarditis, and (3) mitral heart disease.

The history is that of a white male, aged six years, admitted because of a third attack of rheumatic arthritis and carditis. The patient had been in bed several weeks before admission and had lost much weight.

Physical examination revealed an emaciated boy who appeared quite ill, having a temperature of 102° F., an enlarged heart, a loud double mitral murmur and thrill. On the extremities there were many rheumatic nodules (erythema nodosa).

The temperature remained high in spite of salicylate therapy, the legs required casts to straighten the knees, and the patient seemed to be getting worse. On the forty-fifth hospital day, *prontylin*, 7½ grains, was started and given t.i.d. for sixty-six days. Blood culture one week after prontylin was begun showed a streptococcus (type undetermined). Forty-four days after starting prontylin, during which time three transfusions were given because of anemia and high white blood count, the temperature reached normal, where it remained for eighteen days, when the child was transferred to a convalescent hospital. At time of discharge the boy had gained much weight, the sedimentation rate was slightly elevated, and the double murmur

and thrill though present were less intense. Blood cultures were repeatedly negative. No ill effects were noted from use of prontylin nor were there any dramatic changes in patient's condition that would warrant a conclusion of any beneficial effect.

University of Minnesota Hospitals

CASE 1.—Diagnosis: Erysipelas; cellulitis and gangrene of buttocks.

Normal newborn infant (No. 654678), delivered in this hospital Dec. 19, 1936, at full term, without instruments. Weight was 3,150 grams. Physical examination on Dec. 22, 1936, was essentially negative except for an umbilical hernia. On Dec. 24, 1936, a few blebs developed on the medial aspect of the right thigh which were treated with alcohol, 5 per cent silver nitrate, merthiolate, and collodion. Temperature was elevated (101° F.) the following day and reached 104.8° on Dec. 26, 1936. The chest and the ears were negative. Skin lesions became progressively worse, spreading to groins and buttocks, which were markedly inflamed and discolored. The abdomen became distended on Dec. 27, 1936, with a protrusion of the umbilicus.

The baby was transfused on Dec. 30, 1936, with 20 c.c. of citrated whole blood and two days later with 50 c.c. of blood. Fever continued between 103 and 105.4° F. The lesions on the buttocks became gangrenous; Burrow's packs were used in this area.

Prontosil was started on Jan. 2, 1937, and was given intramuscularly, 2 c.c. every four hours for four doses. On the following day, two doses of 2 c.c. were administered, and on January 4, two similar doses were repeated, making a total of eight doses, each of 2 c.c. In addition, one-fourth of one 5 gr. tablet of *prontylin* was given by mouth as follows: two doses on January 4 and four doses on January 5.

There was a marked fall in temperature (to 101.4° F.) immediately after the first dose of prontosil, the temperature going as low as 99.8° after four doses. The child's condition, however, remained serious. The lesions on the buttocks showed no evidence of clearing up, and there was profuse purulent drainage from both buttocks and rectum. On January 5 the baby appeared very listless during the day and more ill than previously. At 9:30 P.M. breathing was labored, and mucus was present in the throat. Death occurred at 10:35 P.M.

Postmortem examination revealed erysipelas, gangrene of the buttocks, and generalized peritonitis. Culture of peritoneal fluid was positive for *B. coli*, nonhemolytic streptococcus, and staphylococcus.

CASE 2.—Diagnosis: Burns, second degree, with secondary infection.

G. K. (No. 656438), a white male, aged three and one-half years, was admitted to the hospital Feb. 23, 1937, five hours after falling into a tub of hot water. Child was in shock, the pulse weak, skin pale, and hands cold and damp. The burned area covered all of the back, part of the abdomen, the right arm and the right leg. Immediate treatment was a transfusion of 250 c.c. of citrated blood, followed by 300 c.c. of intravenous saline. The burns were well tanned with 5 per cent tannic acid solution and then touched with 10 per cent silver nitrate.

For two weeks patient did fairly well. Subcutaneous abscesses then developed in various regions, especially in the extremities and left shoulder. An abscess in left cubital fossa was incised and drained. Culture showed hemolytic streptococci.

A series of treatments with *prontosil* and *prontylin* was given without beneficial effect:

Prontylin, gr. 5, t.i.d.—March 30.
Prontylin, gr. 10, t.i.d.—May 8 to 13.
Prontosil, 5 c.c. once daily intramuscularly from April 1 to 12.

There was a secondary marked infection of the burned areas. A pyogenic arthritis involving the right knee, left shoulder, and left hip developed which was associated with secondary dislocation of the knee, shoulder, and hip. Multiple transfusions were given throughout hospitalization, averaging two each week. In spite of all supportive treatment, patient died on May 22. Autopsy was not granted.

CASE 3.—Diagnosis: Bronchopneumonia, pericarditis, endocarditis, septicemia.

C. M. (No. 644057), a white male, twenty-three months old, entered the hospital March 4, 1937, and died March 15. The history was of attacks of acute abdominal pain associated with fever, dyspnea, and grunting respirations of two weeks' duration; tonsillitis during the week before admission; no nausea, vomiting, or urinary symptoms.

Physical examination showed temperature of 104.6° F., pulse 144, and respirations 26. There was marked irritability and no dyspnea, but the patient preferred to sit up. Eyes and ears were negative. Neck was not stiff. Kernig sign was negative. Lips were dry, tongue was furred, pharynx and tonsils were injected. The cervical nodes were slightly enlarged. Lungs were resonant with a slight diminution of breath sounds at right base. The heart was not enlarged; a systolic murmur was present at apex. Abdomen showed moderate generalized tenderness; liver was tender and palpable 5 cm. below costal margin in midclavicular line.

Laboratory findings were as follows: Urine, negative. Blood with hemoglobin of 70 per cent, leucocytes 22,200, and polymorphonuclear neutrophiles 89 per cent. Tuberculin and Wassermann tests were negative; Schick test was positive. X-rays revealed increased density in left lower lobe behind the heart and no calculi in urinary tract. The impression was lobar pneumonia.

During the hospital course the temperature continued to be septic in type, and the child became progressively worse in spite of multiple transfusions, continuous use of an oxygen tent, high vitamin diet, and sedation. Pneumococcus Type XVIII was isolated from sputum. Several blood cultures were sterile. Agglutinations were negative for *B. typhosus, B. paratyphosus* A and B, Shiga and Flexner types of *B. dysenteriae, Br. melitensis,* and *B. tularense,* and for Felix-Weil reaction. Sinus and mastoid plates were negative. On April 2 the patient developed a skin eruption thought to be a toxic erythema, due to bacterial toxins or drugs. Barbiturates and chloral hydrate were discontinued.

On April 6 *prontosil* was given, 5 c.c. intramuscularly. This was repeated on the seventh and the ninth. *Prontylin,* gr. 5, was given t.i.d. for four days, beginning April 7. This therapy was discontinued when a marked hemolytic anemia developed. Hemoglobin dropped to 30 per cent in spite of transfusions, and patient became jaundiced. The condition continued to be serious; patient became progressively weaker and expired April 10.

Postmortem examination disclosed pericarditis, endocarditis, septicemia, and bronchopneumonia.

CASE 4.—Diagnosis: Acute lymphatic leucemia.

P. S. (No. 656875), a white female, thirteen years old, entered the hospital March 9, 1937, and died May 1, 1937. The chief complaint on admission was stiffness and pain in back from an injury sustained while diving in a swimming pool six weeks previously. She was confined to bed for a month. Illness was associated with fever, pyuria, nocturia, urinary frequency, and pain in the left shoulder and the left hip.

Physical examination revealed a pale, undernourished, not acutely ill girl. Abdomen was tender to deep palpation in left flank. Movements of the spine were limited. There was tenderness over the cervical spinous processes and left sacroiliac joint. The left leg presented a smooth, firm swelling below the middle of the medial aspect, not attached to the skin. Urine showed numerous granular casts and a few white cells. Blood studies revealed a hemoglobin of 72 per cent, leuco-

cytes 12,800 with 65 per cent neutrophiles, 30 per cent lymphocytes, 4 per cent monocytes, and 1 per cent basophiles, and platelets 240,000. Mantoux and Schick tests were negative. Intravenous pyelogram was negative. X-ray examination showed a generalized decalcification of all the bones of the spine with a coarsening of trabeculae. There was a similar process in the pelvis with definite areas of rarefaction around the left hip joint, thought to be osteomyelitic or leucemic. A compression fracture of the fourth thoracic vertebra was noted.

A smear of material aspirated from the mass on the left leg presented a picture typical of lymphatic leucemia. The blood culture was negative. Further roentgenograms showed progressively destructive lesions in all of the bones. Immature cells appeared in the blood smears in increasing numbers. The impression at this time was acute leucemia.

On March 19 *prontylin* therapy was instituted. For eleven days the patient received prontylin, 5 grains, t.i.d. with no improvement.

The patient's condition became gradually worse with a low-grade fever, increased pallor, marked anorexia, weakness, and anemia. The blood picture became more leucemic; lymphocytes increased to 65 per cent; hemoglobin was 34 per cent; and platelets, 165,000. Total leucocytes were 16,000. The patient expired on May 19, 1937, but permission for autopsy was not granted. The final diagnosis was acute lymphatic leucemia.

CASE 5.—Diagnosis: Influenza meningitis.

J. K. (No. 658367), a white female, aged twenty-two months, entered the hospital April 30, 1937, and expired June 8, 1937. Onset of illness was on April 26 with vomiting, anorexia, and fever. Gradually increasing somnolence, swollen, painful right knee, and retraction of the head had been noted shortly before hospitalization.

Physical examination showed the temperature to be 103.6° F., pulse 180, and respirations 70. Further findings were drowsiness, retraction of head, bulging right eardrum, tender, hot, swollen right knee and positive Kernig signs. The spinal fluid was cloudy, not greatly increased in pressure, and had a cell count of 4,500 neutrophiles. Culture showed gram-negative pleomorphic rods—*Hemophilus influenzae*. Laboratory findings were as follows: urine, negative except for 4+ sugar which was not present later; blood—hemoglobin, 63 per cent, leucocytes, 26,900, with 72 per cent polymorphonuclears and 28 per cent lymphocytes.

Spinal punctures were made daily. Influenza serum from Massachusetts State Board of Health was given daily in doses of 12 c.c. intrathecally from May 14 to 27. The spinal fluid cell count fell to 600 on May 3 and as low as 307 on May 15, but became more cloudy after that date. Five blood transfusions were given during the course of the illness. Bilateral myringotomy was necessary on two occasions.

Prontylin therapy was instituted on the day of admission. This medication was given in 10 grain doses with 10 grains of sodium bicarbonate. Patient received 20 grains of prontylin the first day, 10 grains on the second day, 30 grains on the third day and 40 grains on every day thereafter (10 grains q.i.d.) until May 14. Prontylin was started again on May 17 with a total of 30 grains daily: 10 grains at 6 A.M. and at noon, and 5 grains at 6 P.M. and at midnight. This dosage was continued until May 27, when all prontylin therapy was discontinued. On that day a bright red rash appeared on forehead, arms, wrists, ankles and feet which was felt might be due to prontylin. The following day the wrists were ecchymotic.

During the first two weeks patient was clinically somewhat improved, but then became progressively worse and died June 8, 1937. Postmortem examination revealed purulent meningitis, most marked at the base of the brain.

CASE 6.—Diagnosis: Acute rheumatic fever; acute appendicitis.

R. C. (No. 658606), a white male, fourteen years old, was admitted to the hospital on May 10, 1937, and is still hospitalized (June 23). There was a history of epigastric pain and vomiting of three days' duration, but of no previous attack and no joint pains.

Temperature was 100° F., pulse, 100, and respirations, 22. Physical examination showed an acutely ill boy, with cheeks flushed, throat moderately injected, some enlargement of cervical glands, lungs clear, and heart negative. There was moderate tenderness near midline below umbilicus, but no rigidity or rebound tenderness. Laboratory reported negative urine and blood with 94 per cent hemoglobin, 12,900 leucocytes, 85 per cent neutrophiles, and 15 per cent lymphocytes. It was believed that patient had acute appendicitis. Appendectomy was performed, the appendix showing subsiding stage of an acute attack.

On May 12 he complained of pain in right knee. On the following day the left knee was involved. A diagnosis of acute rheumatic fever was made and salicylates were ordered. Temperature which had been ranging from 100 to 102° approached normal for several days thereafter, but has since been running a spiking course. Severe sore throat developed on June 7, associated with profuse nasal discharge and obstruction. Swallowing became difficult. Peritonsillar abscess ruptured spontaneously on June 13; after this his condition has been gradually improving. Medication has consisted of 30 grains sodium salicylate and 30 grains sodium bicarbonate daily, ephedrine nose drops, hot saline throat irrigations, and *prontylin*. Prontylin therapy was instituted on June 14. Patient has been and is still getting 5 grains t.i.d. For the past two days the temperature is essentially normal, and the child is clinically greatly improved.

CASE 7.—Diagnosis: Mastoiditis, left; meningitis.

LeR. S. (No. 658796), a white male, aged nine years, was admitted May 16, 1937, and was discharged June 16, 1937. There was a history of measles, onset on May 6, associated with coryza, conjunctivitis, and severe cough. Earache developed May 12, and with it pain over the mastoid process and zygomatic region. During two days before admission the fever had been high, the left ear had been discharging profusely, and the neck was stiff.

The temperature on admission was 104.2 °F., pulse 120, and respirations 24. Physical examination revealed an acutely ill boy with flushed face, swelling over left ear, and severe pain over left zygoma and mastoid areas. The left ear was discharging, the right ear negative. The throat was reddened, with exudate on the tonsils. The lungs were clear, the heart and the abdomen negative. The neck was stiff; the spine was unable to be flexed; and Kernig signs were positive.

Laboratory findings were as follows: urine, negative; blood with 84 per cent hemoglobin, 30,600 leucocytes and 84 per cent polymorphonuclears, and sugar 86 mg. per cent. Culture of spinal fluid was sterile. Roentgenograms showed acute mastoiditis with destructive mastoiditis on the left, and localized mastoiditis on the right. Diagnosis was made of left mastoiditis, including zygomatic mastoiditis and meningitis.

Left mastoidectomy was done immediately. A subperiosteal abscess was encountered. The cell structure in the zygoma was also removed.

Two blood transfusions were given, 300 c.c. on May 17 and 200 c.c. on May 20. *Prontylin*, 10 grains q.i.d., was started on May 17 and continued for sixteen doses. During this period there was some cyanosis which was thought might be due to this medication. Prontylin was not discontinued, however, until the temperature became normal on May 21. Since that date patient had an uneventful course and was discharged in good condition on June 16.

CASE 8.—Diagnosis: Upper respiratory infection; cervical adenitis; erysipelas; synovitis, streptococcal.

R. O. (No. 658887), a white female, aged seventeen months, was admitted to the hospital May 18, 1937, and is not yet discharged (June 23). A history was obtained of upper respiratory infection of four days' duration, with profuse mucopurulent nasal discharge, nasal obstruction, sore mouth, and irritability. Cervical glands were enlarged; the appetite was poor; there were fever of 102° F. and dyspnea.

Physical examination showed temperature of 103.8°, pulse 44, and respirations 32. The child appeared acutely ill; the respirations were noisy; the nasal discharge was profuse and mucopurulent, but not bloody. The eardrums were dull, not bulging; the tonsils were markedly enlarged and reddened; the pharynx was injected. No membrane was visible, nor retropharyngeal abscess palpable. There was bilateral enlargement of cervical glands. The lungs were clear; the heart and the abdomen, negative.

Laboratory findings showed urine negative except for a trace of albumin, and blood with hemoglobin 75 per cent, leucocytes, 32,400 with 79 per cent neutrophiles. Schick test was positive; tuberculin and Wassermann tests were negative.

Therapy has consisted of sedation, steam inhalations, ice collar, ephedrine nose drops, and atropine sulphate on two occasions. On May 23 the left knee became red and swollen, with well demarcated margins—appearing like erysipelas. An ultraviolet ray treatment was given at 11 A.M. and *prontylin* started at 8 P.M., 10 grains t.i.d. This medication was continued for six days. The lesion of the knee spread to the back of the knee, but on May 24 it was improved and soon faded.

The patient had a stormy course for two weeks, then had a week of comparatively normal temperature with the upper respiratory infection practically cured. Since June 7, the temperature has been spiking up to 101 or 102°. Right shoulder became markedly swollen and tender to palpation. X-ray films revealed fluid in the joint. This was aspirated, and yellowish, nonpurulent fluid was obtained. Culture is not yet reported. On June 22 the right arm and shoulder were immobilized in a cast.

CASE 9.—Diagnosis: Lymphatic leucemia; impetigo contagiosa.

K. K. (No. 624184), a white female aged three and one-half years, entered the University Hospital May 19, 1937, and died June 19, 1937. The history revealed that during the past winter there was insidious onset of increasing lassitude, anorexia, pallor, and weakness. There was recent low-grade fever, profuse perspiration, and pain in right arm and left leg. On May 7 the patient was hospitalized in St. Mary's Hospital, where a diagnosis of lymphatic leucemia was made. The temperature was 101.2° F., pulse 110, and respirations 22. Past history was nonessential.

Physical examination showed irritability, marked pallor, recent loss of weight, slight icterus, but no petechiae. The lungs were clear. The heart had loud blowing systolic murmur over precordium. The abdomen was moderately enlarged; the liver's edge, halfway between costal margin and umbilicus; the spleen not palpable. Urine was negative. A blood count revealed hemoglobin of 27 per cent, white cells, 2,400; neutrophiles, 32 per cent; lymphocytes, 65 per cent; monocytes, 1 per cent; and basophiles, 2 per cent. Reticulocytes were 11.1 per cent, and platelets numbered 125,420. X-ray films of the long bones, pelvis, and skull showed leucemic infiltration. The impression was lymphatic leucemia.

The early course in the University Hospital was favorable. Ferric ammonium citrate was started as medication on May 23. Clinically the patient was markedly improved, appearing alert and interested in play. The liver decreased in size. On June 13, 3 c.c. of Lederle's liver extract was given intramuscularly. The following day patient developed impetiginous vesicles on right thigh and left buttock. These rapidly spread over back and lower extremities with initial formation of large

bullae. Temperature rose to 106°. The lesions were treated with 10 per cent silver nitrate and 5 per cent ammoniated mercury. A large bullous lesion beneath right eye soon involved right cheek. Culture of vesicular fluid showed staphylococcus.

Prontylin therapy was instituted on June 10, 10 grains q.i.d. Ten doses of this drug were given by mouth. Patient's temperature remained elevated, between 102° and 104°, and pulse from 140 to 180. She was unable to take fluids. Her condition became more serious, and she expired June 19. Permission for autopsy was not granted.

CASE 10.—Diagnosis: Chronic osteomyelitis, acute exacerbation; bronchopneumonia; pericarditis.

R. C. (No. 651284), a white male, aged fourteen years, was readmitted to the hospital June 17, 1937, acutely ill, and still hospitalized (June 23).

First admission was from Aug. 12, 1936, to Dec. 18, 1936, for treatment of an acute osteomyelitis of right tibia, which had spontaneously ruptured and was draining purulent material from two sinuses. X-ray films later revealed marked destruction of the bone. Patient had a rather stormy course and on Nov. 18, 1936, a sequestrum of the right tibia was removed. A cast was applied to the leg, and the boy was discharged in fair condition.

Since then patient has returned four times for a change of cast. On one occasion a second sequestrum was removed. His last admission was from June 4 to 7, 1937. On discharge child's condition was quite good.

The present illness began about thirty hours before admission with chills, vomiting, rapid respirations, and fever. There was a tender swelling on the anterior aspect of right thigh just below inguinal ligament. Pain radiated down the leg. On admission the temperature was 105.6°, pulse 146, and respirations 38. The patient was irrational. Physical examination showed dry, hot skin, precordial friction rub, impaired breath sounds, and tenderness of right ankle and foot. The urine was negative. Blood count showed hemoglobin, 90 per cent, leucocytes, 7,900, with 88 per cent neutrophiles. X-ray of chest revealed bilateral pneumonia.

Patient has been treated with multiple blood transfusions and 5 per cent glucose intravenously. He has been in an oxygen tent continuously. Temperature which reached 106.6° at 8 A.M. June 17 was 104° at 6 P.M. The first dose of *prontylin* was given at 6:30 P.M., 450 c.c. of 0.8 per cent solution intravenously. By 10 P.M. temperature was 101°. This rose to 104.4° the following day, but was gradually falling and was normal for the first time at 11 P.M. on June 19. The second dose of prontylin was 350 c.c. of 0.8 per cent solution, given intravenously at 2:30 P.M. June 18. At 6:30 P.M. on the same day 450 c.c. of a similar solution was given. On June 19 at 2 P.M. 350 c.c. of 0.8 per cent prontylin was given intravenously. The patient appeared clinically greatly improved, became rational, and was able to do without an oxygen tent. Since then prontylin has been given by mouth only, two doses of 20 grains each on June 21 and four doses of 10 grains each on June 22 and 23. The temperature has been normal for four days, and patient at present is doing very well.

CLINICAL EXPERIENCE IN THE USE OF SULFANILAMIDE AT THE NEW HAVEN HOSPITAL

P. O. Hageman, M.D.
New Haven, Conn.

DURING the past six months a variety of infectious conditions have been treated with sulfanilamide on the pediatric service of the New Haven Hospital (Table I). With the exception of beta-hemolytic streptococcic infections our experience has been very limited. The streptococcic infections as listed in Table I are included along with the cases from other services in a report being published by the Department of Medicine.[1]

Table I

Cases Treated With Sulfanilamide

BETA-HEMOLYTIC STREPTOCOCCIC INFECTIONS		60
Erysipelas	6	
Pneumonia	5	
Meningitis	1	
Mastoiditis	12	
Otitis media	9	
Sinusitis	4	
Tonsillitis	7	
Cervical adenitis	7	
Scarlet fever	8	
Rheumatic fever	1	
MISCELLANEOUS INFECTIONS		8
Gonococcic ophthalmia	1	
Gonococcic vaginitis	3	
Staphylococcic septicemia	1	
H. influenza meningitis	1	
B. coli pyuria	1	
Typhoid fever	1	
	Total	68

Beta-hemolytic streptococcic infections:

Erysipelas.—All cases responded satisfactorily within forty-eight hours. Two cases of erysipelas in newborn babies with positive blood cultures showed dramatic recoveries. One of these developed an abscess after the drug was discontinued; after incision and drainage was performed recovery was prompt.

Pneumonia.—Three of the five cases of pneumonia had empyema when treatment was instituted. In these instances the severity of the disease was favorably modified, but contraction of the chest and thickening of the pleura created difficult therapeutic problems. Two of the three re-

From the Department of Pediatrics, Yale University School of Medicine.

quired thoracotomy. Two cases without empyema responded satisfactorily. All cases recovered.

Meningitis.—The spinal fluid which was heavily infected in this case when treatment was instituted, became sterile in forty-eight hours. Internal hydrocephalus developed during convalescence even though the infection had long since subsided.

Mastoiditis.—Eight cases of mastoiditis subsided without surgical treatment. Only one case required operation after treatment was started. In the remaining three cases operation was performed on admission. The most dramatic recovery without operation occurred in a case with destructive mastoiditis and meningeal irritation (4,000 cells in the spinal fluid).

Otitis Media.—Two cases subsided without developing discharge. Myringotomy was performed before sulfanilamide was started in three instances. No myringotomies were done after treatment was instituted. Mastoiditis did not develop in any of the nine cases. The drug appeared to shorten the course of the disease in all but one instance.

Sinusitis.—Four cases of sinusitis responded satisfactorily without surgical intervention.

Tonsillitis.—The immediate therapeutic result was excellent in seven cases, but beta-hemolytic streptococci persisted in throat cultures in some instances, as long as four and five weeks.

Cervical Adenitis.—One of seven cases required incision and drainage. Relapse occurred in one instance, but response to a second course of sulfanilamide was satisfactory. The remaining cases subsided promptly.

Scarlet Fever.—In a group of eight cases, the toxic phase of the disease seemed unaffected by sulfanilamide therapy. No septic complications occurred, however.

Rheumatic Fever.—This patient had severe cardiac involvement and expired several days after sulfanilamide was started.

Miscellaneous Infections.—One case of gonococcic ophthalmia developed a negative conjunctival smear thirty-six hours after sulfanilamide was started. Of three cases of gonococcic vaginitis the courses of two seemed unaffected and the third responded very satisfactorily. Sulfanilamide had no effect in one case of staphylococcic septicemia. Influenzal meningitis treated with sulfanilamide ran its natural course and terminated fatally in one case. Colon bacilluria cleared completely in forty-eight hours in one instance. A case of typhoid fever, which is still under treatment, has shown no beneficial effects from the drug.

Dosage.—When practicable, sulfanilamide given orally was the preferred method of administration. In general, 1 gram per day per 20 pounds of body weight (with a maximum of 4.8 grams per day) was given in divided doses at six-hour intervals. Parenteral sulfanilamide was given

subcutaneously and intrathecally in 0.8 per cent solution in physiologic saline. The dosage of sulfanilamide for subcutaneous administration was 0.8 gram per 40 pounds of body weight per day, given in divided doses at twelve-hour intervals. Prontosil has been discarded in favor of crystalline sulfanilamide because the latter seems more effective and convenient and is less expensive.

Reactions to Sulfanilamide.—The incidence and types of reactions encountered are being described in detail in a separate communication.[2] Cyanosis associated with methemoglobinemia was encountered in approximately 50 per cent of the cases treated. Fever coming on seven to ten days after institution of sulfanilamide therapy was noted in one of every six cases treated. In approximately one-half of the cases showing this febrile complication, there was an accompanying morbilliform rash. Recovery was prompt in each instance after the drug was discontinued. No cases of neutropenia were noted.

Summary.—The results presented along with impressions gained during this study indicate that sulfanilamide is a useful, though not harmless, chemotherapeutic agent in the treatment of beta-hemolytic streptococcic infections. Data on the efficacy of sulfanilamide in other types of infection are too meager to warrant the expression of an opinion.

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REPORT ON THE USE OF SULFANILAMIDE AT THE CHILDREN'S HOSPITAL OF MICHIGAN

S. S. Bernstein, M.D.
Detroit, Mich.

Streptococcic Infections

Meningitis

Case 1.—B. B., female, aged six months, weighing 8.2 kilograms, was admitted on May 20, 1937, with a history of high fever and lethargy for two days. She was critically ill, semicomatose with paralysis of the left side of the face, the left arm, and the left leg. The fontanel was full and her neck, stiff. The spinal fluid was cloudy with 2,200 polymorphs per cubic millimeter. The culture was positive for *Streptococcus hemolyticus.*

Sulfanilamide therapy was started at once; 45 grains by mouth, 9 grains subcutaneously, and 3 grains intraspinally were given daily.

The patient showed no improvement. The fever, which was 104° F. on admission, rose to 105° on the third hospital day, and the child expired.

The sulfanilamide level in the blood on May 29, 1937, was 11.8 mg. per cent and in the spinal fluid it was 9.0 mg. per cent.

Otitis and Mastoiditis

Case 2.—D. L., male, aged eight months, weighing 16½ pounds, who had been discharged following a right mastoidectomy two weeks previously, was readmitted on June 3, 1937, with a history of high fever and swelling around the mastoidectomy wound for two days.

Temperature on admission was 105° F., and there was a definite cellulitis around the mastoid wound. Culture of wound was positive for *Streptococcus hemolyticus.* Sulfanilamide, 15 grains orally, was given daily. The temperature curve dropped to normal within twenty-four hours and remained flat.

The cellulitis cleared up rapidly. The patient was discharged on June 8, 1937.

Case 3.—J. T., female, aged nine months, weight 10 pounds. The patient had a right mastoidectomy on April 20, 1937; following the operation, the temperature was below 101° F. until April 24, when an erysipeloid lesion appeared around the mastoid wound. The temperature rose to 105° F. Culture of the wound was positive for hemolytic streptococcus.

On April 27 sulfanilamide was started, 10 grains (orally) being given daily.

On May 3, 4, and 5, an additional 18 c.c. of prontosil was given intramuscularly. A transfusion was given on April 28.

On May 3 the spread of the cellulitis stopped, and on May 5 the temperature curve, which had been fluctuating between 101 and 105° F., reached normal and remained flat. The cellulitis cleared rapidly, and the patient was discharged May 13.

Case 4.—H. S., white, male, aged seven and one-half years, weighing 60 pounds, was admitted April 29, 1937, with a history of suppurative otitis media for eighteen days on the right side and for eleven days on the left side. Temperature on admission was 105° F. The day following admission patient began to complain of swelling and pain in the left hip and the left wrist. Blood culture taken at this time was positive for a hemolytic streptococcus. The same organism was found in the ears.

On May 1 a bilateral mastoidectomy was done. The temperature remained between 102 and 105° F. On May 4, 5, and 6, the patient received small transfusions. On May 4, 60 c.c. of prontosil was given intramuscularly with 15 grains of sulfanilamide orally. For the next ten days 35 grains of sulfanilamide were given daily.

On May 7 the temperature reached normal and remained there. The pains in the hip and the wrist improved rapidly. Patient was discharged on June 8.

CASE 5.—P. P., female, aged seven months, weighing 15½ pounds, was admitted April 12, 1937, with a history of profuse aural drainage and diarrhea for one week. The ear cultures were positive for *Streptococcus hemolyticus*. The ears drained continuously.

On May 17 a right mastoidectomy was performed, and on May 20 a left mastoidectomy was done. The patient became very toxic. The temperature rose to 103° F. and remained high.

Sulfanilamide started on May 27 with an initial dose of 15 grains (orally) and then 5 grains every four hours. This was continued for one week. The temperature began to drop within twenty-four hours after the sulfanilamide was started and reached normal in another twenty-four hours, where it remained until discharge June 14.

CASE 6.—W. K., white, male, aged six and one-half years, weight 65 pounds. A right mastoidectomy was performed on April 8, 1937; culture of the wound was positive for a nonhemolytic streptococcus. On April 9 a cellulitis appeared around the mastoid wound, the temperature rising to 104° F. and remaining between 104 and 105° until April 13, when the patient received 30 c.c. of prontosil intramuscularly and 20 grains of sulfanilamide orally. This was followed by a temperature drop to 101° F. The sulfanilamide was continued for five days. The temperature curve became normal on the third day of sulfanilamide therapy and remained flat. The cellulitis cleared rapidly. The patient was discharged April 21.

Mastoiditis and Pneumonia

CASE 7.—A. B., colored, female, aged six months, weighing 7½ kilograms, was admitted on March 18, 1937, with bronchopneumonia and bilateral otitis media. On April 7 erysipelas appeared on the scalp. The temperature rose from 102 to 104° F. Signs of pneumonia had persisted throughout this period. The patient received a blood transfusion on April 8. On that day prontosil 2.5 c.c. intramuscularly every four hours was started, and also sulfanilamide 10 grains daily was given.

Both of these were discontinued on April 22. Blood counts during this period showed a moderate hypochromic anemia with white counts varying from 5,000 to 8,000, with 60 to 70 per cent polymorphonuclears. The patient showed only slight improvement although the erysipelas cleared up; the temperature remained around 103° F.

Bilateral mastoidectomy (cultures positive for *Streptococcus hemolyticus*) was performed on May 5. Transfusions were given, and sulfanilamide was started again on that day in the same doses as above. On May 7 the patient became jaundiced (icteric index, 60). After a very stormy course over a period of five days, the temperature again returned to normal, where it stayed for one week. The patient's pneumonia, however, was not improved, and some jaundice was present. The sulfanilamide was again discontinued on May 17. Almost at once the temperature rose to 104° F. The pneumonia extended, and the jaundice deepened. Sulfanilamide was started again on May 20 but was stopped almost at once when it was found that the white blood count showed no polymorphonuclear leucocytes.

Intramuscular liver, transfusions, and pentnucleotide failed to improve the granulopenia, and the patient expired on May 29.

Adenitis and Erysipelas

CASE 8.—B. H., male, aged five years, weighing 36 pounds, was admitted Feb. 12, 1937, with a history of a sore throat and a high fever for one week. On physical examination follicular tonsillitis and a large cervical adenitis on the left side were found. Temperature on admission was 104° F. The throat culture was positive for hemolytic streptococcus. Three small transfusions were given with no clinical improvement. The temperature peak reached 105° F. daily. On the fourth hospital day erysipelas appeared on the left cheek.

Thirty cubic centimeters of prontosil were given intramuscularly on each of the next three days. Then 10 c.c. of prontosil with 18 grains of prontylin (orally) was given for the next two days, followed by 18 grains of prontylin daily for 6 days.

The erysipelas stopped spreading within twenty-four hours after the prontosil was started. The cervical adenitis was drained on the seventh hospital day. The temperature began to drop shortly after the prontosil was started, reached normal on the tenth hospital day, and remained flat thereafter. Patient was discharged on the sixteenth day in the hospital.

Peritonitis and Septicemia

CASE 9.—M. L., male, aged six years, was admitted on Dec. 17, 1936, with a history of sudden onset of abdominal pain and vomiting that day. Temperature on admission was 106° F. The abdomen was distended, with generalized rigidity and tenderness.

The blood culture and culture of the abdominal fluid both yielded a hemolytic streptococcus. Patient received daily transfusions of whole blood. Intramuscular prontosil was given as follows: 15 c.c. on the second day; 30 c.c. on the third day; 35 c.c. on the fourth day and the fifth day.

There was no improvement, and the patient died on the seventh day.

MENINGOCOCCIC INFECTIONS

Meningitis

CASE 10.—M. P., male, aged five months, weighing 8.1 kilograms, was admitted May 19, 1937, almost moribund with a history of high fever, stupor, and purpura for forty-eight hours. The patient's neck was stiff; the fontanel was bulging; and in the skin there were many petechiae and purpuric spots.

The blood count showed a hemoglobin of 7 gm. with 2,800,000 red blood cells. No platelets could be seen in the smear. On spinal puncture the fluid was cloudy with 9,000 polymorphs. Smear and culture were both positive for meningococcus.

Patient received a transfusion with 150 c.c. of whole blood at once. In the first twenty-four hours 40 grains of sulfanilamide were given by mouth and 12 grains interstitially. This dose was repeated on the two following days, and then 20 grains were given by mouth with no interstitial dose for the next two weeks.

The sulfanilamide level of the blood was 3.09 mg. per cent on May 25 and 17 mg. per cent on June 1. The level in the spinal fluid was 2.74 mg. per cent on May 25, 12.6 mg. per cent on June 1, and 5 mg. per cent on June 4.

Clinically the patient improved very slowly, but steadily. The temperature dropped by lysis over a period of two weeks. The spinal fluid findings cleared slowly, returning to normal after three weeks. The platelets returned to normal, but the anemia has persisted.

CASE 11.—C. V., female, aged seventeen months, weighing 24 pounds, was admitted on May 12, 1937, with a history of petechiae and fever for ten days. She was vomiting and had a stiff neck on the day of admission.

Physical examination revealed a very toxic child with a stiff neck and positive Kernig's and Brudzinski's signs. The spinal fluid was cloudy with 2,000 polymorphs per cubic millimeter. Smear and culture were positive for meningococci.

Twenty thousand units of meningococcus antitoxin were given intravenously, and 30 c.c. of Michigan state antimeningococcus serum was given intraspinally; this latter was repeated the next day.

On admission 15 c.c. of prontosil was given intramuscularly and 30 grains of sulfanilamide (orally). The 30 grains were repeated daily for eighteen days.

Small blood transfusions were given on May 15, 16, and 17.

The temperature remained high for the first four days and then dropped by lysis to reach normal on the tenth day, where it remained as the patient went on to an uneventful recovery.

The sulfanilamide levels in the blood were 2.6 mg. per cent on May 24; 4.5 mg. per cent on May 26, and 8 mg. per cent on June 1.

The sulfanilamide was discontinued on June 1 because of a moderate granulopenia. The original white count was 20,200 with 76 per cent polymorphonuclears. This dropped to 14,800 with 20 per cent polymorphs. The count quickly returned to normal after medication was discontinued. The hemoglobin level and red cell count were normal throughout.

THE USE OF PARA-AMINOBENZENESULFONAMIDE AND ITS DERIVATIVES IN THE TREATMENT OF INFECTIONS DUE TO THE β STREPTOCOCCUS HEMOLYTICUS, THE MENINGOCOCCUS, AND THE GONOCOCCUS

Report of 38 Cases

Benjamin W. Carey, Jr., M.D.
Boston, Mass.

IN THIS preliminary report we wish to record our experiences with para-aminobenzenesulfonamide and its derivatives in the treatment of patients with infections caused by the β hemolytic streptococcus, the meningococcus, and the gonococcus.

Prior to the report of Long and Bliss,[1] the dosage and method of administration of para-aminobenzenesulfonamide and its derivatives at the Infants' and Children's Hospitals were not on a standard basis. Following the publication of this paper the plan of treatment used was as follows:

By mouth: Prontylin tablets; 0.045 gm. per pound of body weight per twenty-four hours, divided into four or six doses.

Intramuscularly: Prontosil solution (2.5 per cent aqueous); 1 c.c. per pound of body weight per twenty-four hours, divided into four or six doses.

Subcutaneously or intravenously:* Para-aminobenzenesulfonamide, 0.8 per cent in physiologic salt solution; 100 c.c. per 40 pounds of body weight every eight or twelve hours.

Intrathecally: Para-aminobenzenesulfonamide, 0.8 per cent in physiologic salt solution; 10 c.c. less than the volume of cerebrospinal fluid withdrawn by lumbar puncture.

If prontosil and prontylin were administered together the dose of each was reduced one-half from the above estimated amounts.

After the publication by Marshall[2] of the method for estimating the concentration of para-aminobenzenesulfonamide in blood and urine we found that the blood concentration of para-aminobenzenesulfonamide in patients receiving the drug according to the Long and Bliss[1] plan of treatment reached a level of only 4 to 7 mg. per cent after several days of therapy, at a time when the blood level had supposedly reached its maximum concentration. Therefore the dosage was revised as follows:

By mouth: Prontylin tablets; an initial dose of 0.6 gm. for each 20 pounds of body weight; followed by a maintenance dose of approximately

From the Department of Pediatrics and the Department of Bacteriology and Immunology of the Harvard Medical School, and the Infants' and Children's Hospitals.

*Para-aminobenzenesulfonamide was given intravenously to three patients for whom subcutaneous injections were not feasible. Intravenous administration does not appear to be advisable unless the condition of the patient prevents the use of subcutaneous injections. Two of the patients treated intravenously developed a febrile reaction which seemed to be an effect of the drug.

0.06 gm. per pound of body weight per twenty-four hours, divided into four or six doses.

Subcutaneously or intravenously: Para-aminobenzenesulfonamide, 0.8 per cent in physiologic salt solution; an initial injection of 100 c.c. per 20 pounds of body weight; followed by maintenance injections of 100 c.c. per 40 pounds of body weight every eight or twelve hours.

Following this revised dosage the concentration of para-aminobenzenesulfonamide in the blood of patients receiving the drug was maintained at or around the level of 10 to 15 mg. per cent, so far as possible.

No definite rule has been made as to the time of discontinuing the drug, as each patient needs individual treatment. In general, the plan was to reduce the maintenance dose of prontosil or prontylin by one-half one to three days following definite clinical improvement and the disappearance of the organisms. This dose was then continued for one to two weeks, depending upon the general appearance of the patient and upon the absence of reactions which could be ascribed to the drug. In the event of reappearance of the organisms treatment was then continued with a dose according to the circumstances.

In previous reports,[1, 3, 4] the toxic symptoms attributed to para-aminobenzenesulfonamide or its derivatives have included cyanosis, nausea and vomiting, fever, lassitude and headache, and hematuria. In unpublished reports there have been added hemolytic anemia, agranulocytosis, acidosis, skin rashes, and jaundice. Reactions attributed to the drug in the present group of patients included cyanosis, fever, lassitude and headache, possibly hemolytic anemia, acidosis, and jaundice. However, it is very questionable whether the jaundice observed in one patient was an effect of the para-aminobenzenesulfonamide. Agranulocytosis, nausea and vomiting, hematuria, or skin rashes have not been observed in this series of cases.

The salient features of the patients whom we have treated in the six-month period ending June 15, 1937, with para-aminobenzenesulfonamide and its derivatives are presented in the case abstracts.

SUMMARY

Meningococcus Meningitis.—(Cases 1-5.) There were five patients with meningitis due to the meningococcus in whom antimeningococcus serum was not used. Only one of these five patients, Case 1, received para-aminobenzenesulfonamide intrathecally. Patients 3 and 4 received para-aminobenzenesulfonamide intravenously. The duration of the meningitis before treatment varied from one to five days. The duration of treatment varied from four to ten days. In all patients cultures of the cerebrospinal fluid were sterile after twenty-four hours of treatment and there were no recurrences of the bacteria in the cerebrospinal fluid. In three of the patients the meningococcus was cultured from the blood. A blood culture was not taken in two of the patients. Four of the five patients developed cyanosis of the lips and nail beds within forty-eight

hours after starting treatment. One of the patients complained of a severe generalized headache three days after treatment was begun. The headache disappeared twenty-four hours after therapy was discontinued. This patient also was slightly drowsy with the duration of the headache. Two patients treated intravenously had a temperature of 100° to 101° F. and one was drowsy during the entire time of therapy. The temperature became normal twelve hours after treatment was discontinued. There were no deaths in this group and no sequelae of the meningitis were noted.

Erysipelas.—(Cases 6-14.) In the group of nine patients with erysipelas there were two deaths. In one patient who died, the β hemolytic streptococcus had been cultured from the blood and death occurred after twelve days of treatment. The other patient died of a congenital malformation of the heart. Septicemia did not occur in the remaining 7 patients. In the 7 patients who recovered, the spread of the erysipelas halted within eighteen hours after therapy was started and the lesion of the skin had faded by the third day. Cyanosis of the lips and nail beds was noted in 6 patients. Patients 13 and 14 were cyanotic before treatment was started, the former from general circulatory disturbances as a result of the infection and the latter as a result of the congenital malformation of the heart. Patient 7 had marked hyperpnea on the third day of treatment. The hyperpnea promptly disappeared at cessation of therapy. Icterus of the skin and mucous membranes was noted the eighth day after treatment had begun in patient 13. Necropsy revealed a generalized infection with the β hemolytic streptococcus and the presence of an acute hepatitis and marked biliary stasis. The icterus in this patient probably could not be attributed to the effect of the drug.

Peritonitis.—(Cases 15-18.) There were 4 patients with peritonitis caused by the hemolytic streptococcus, all of whom died. One patient had an abscess of the liver which was incised and drained, in addition to peritonitis. Incision and drainage of the peritoneal cavity was done on the other 3 patients. Two patients developed cyanosis of the lips and nail beds, presumably an effect of the drug.

Vulvovaginitis.—(Cases 19, 20.) Two patients with vulvovaginitis caused by the gonococcus were treated with prontylin. The vaginal discharge and bacteria disappeared after three days of therapy in 1 patient and had not recurred three months later. The vaginal discharge disappeared and no bacteria could be found in a stained smear from the vagina of the other patient after five days of treatment. Four days later the discharge became profuse and bacteria were present. The drug was continued and three weeks later the vaginal discharge had decreased in amount but bacteria remained present. This patient had cyanosis of the lips and nail beds after two days of therapy.

Meningitis Secondary to Mastoiditis.—(Cases 21-24.) There were 4 patients with mastoiditis complicated by meningitis. The β hemolytic streptococcus was cultured from the mastoid in all four patients. In 2

of these patients the β hemolytic streptococcus was also cultured from the cerebrospinal fluid. The cerebrospinal fluid became sterile after twenty-four hours of treatment in each case. In the other 2 patients no bacteria were cultured at any time from the cerebrospinal fluid. After the fifth day the temperature was normal in each of these 4 patients. Cyanosis of the lips and nail beds was noted in the 4 patients twenty-four hours after therapy was started. There were no deaths in this group.

Peri-sinus Abscess and Mastoiditis.—(Case 26.) One patient had a peri-sinus abscess complicating mastoiditis and recovered. The peri-sinus abscess was incised and drained at the time of the mastoidectomy. Prontosil and prontylin were started immediately following the operation. The temperature was normal after the third day and the patient made an uneventful recovery. Cyanosis of the lips and nail beds was observed in this patient.

Acute Otitis Media.—(Cases 27-34.) There were 8 patients with acute otitis media who received these drugs. Two of these patients had mastoidectomy done after adequate therapy had been given. Patient 27 received prontylin for seven days after admission to the hospital and the mastoidectomy was done three weeks later. No reactions were observed in this patient which might be attributed to the drug. Patient 28 had otitis media associated with scarlet fever and received prontylin for eighteen days. The culture of the discharge from the ear became sterile during the therapy but repeated x-ray examination of the mastoid revealed increasing destruction of the cells and it was necessary to do a mastoidectomy. In 3 of the other 6 patients the otitis media subsided during treatment with prontylin, in one week or less. In 1 patient the ear discharged for two weeks, in 1 for three weeks, and in 1 for six weeks. Cyanosis of the lips and nail beds was noted in 6 patients of this group. In addition drowsiness was observed in patient 29 after receiving prontylin for five days. No deaths occurred in this group of 8 patients.

Septicemia.—(Cases 35-38 and Case 25.) There were 5 patients with septicemia caused by the hemolytic streptococcus. In 2 patients the infection had already localized in one or more joints before therapy was started. Patient 35, with an acute arthritis of the hip joint, received treatment for seventy-eight days. Slight cyanosis of the lips and nail beds was the only reaction to the drugs observed in this patient. Patient 37 had a sterile blood culture after receiving prontylin twenty-four hours and the temperature was normal on the third day. The septicemia in patient 38 followed an infection in a lesion of the arm caused by a clothes wringer. Blood cultures were positive on 2 successive days after admission to the hospital. Prontosil and prontylin were started the third day. The temperature became normal after twenty-four hours of therapy and a culture of the blood was sterile. Four weeks later this patient developed acute tonsillitis, cervical adenitis, and hemorrhagic nephritis. He re-

mained in the hospital two and one-half months and was well at the time of discharge. Cyanosis of the lips and nail beds was observed in the 4 patients of this group. Patient 37 in addition was noted to have hyperpnea after receiving prontylin for five days and the carbon dioxide combining power of the blood was 37 vol. per cent. The erythrocytes of the blood of this patient dropped from 5,000,000 to 2,000,000 per c.mm. after receiving prontylin for ten days. Patient 25 had septicemia and lateral sinus thrombosis complicating mastoiditis. The β hemolytic streptococcus was cultured from the blood on 6 occasions in the ten days following the mastoidectomy and ligation of the internal jugular vein. Prontosil and prontylin were given during this time and for five days following the last positive blood culture. Cyanosis of the lips and nail beds was noted. There were no deaths in this group of patients.

TOXIC REACTIONS

As mentioned above, the reactions to para-aminobenzenesulfonamide and its derivatives which we have observed are: Cyanosis in 31 patients; acidosis in 2 patients; fever in 2 patients; anemia in 1 patient; headache and drowsiness in 3 patients; and jaundice in 1 patient, but at necropsy generalized β hemolytic streptococcus infection, acute hepatitis and marked biliary stasis were discovered, so it is questionable that the jaundice was caused by the para-aminobenzenesulfonamide.

We have not seen agranulocytosis, skin rashes, nausea and vomiting, or hematuria in patients receiving para-aminobenezenesulfonamide or its derivatives.

CONCLUSIONS

Our experience tends to support the usefulness of para-aminobenzenesulfonamide and its derivatives in the treatment of infections due to the β hemolytic streptococcus, the meningococcus, and the gonococcus.* But definite conclusions should not be drawn until there is further clinical and laboratory evidence as to the proper dosage, the optimum concentration of para-aminobenzenesulfonamide in the blood, and further information regarding the nature of the reactions which may be encountered.

Certainly for the present it is inadvisable to use these chemical substances in the treatment of infections caused by bacteria other than the β hemolytic streptococcus, the meningococcus, and the gonococcus until there is sufficient clinical and experimental laboratory evidence supporting their use.

The prontosil, prontylin, and para-aminobenzenesulfonamide used in the treatment of these patients were donated by the Winthrop Chemical Company, Inc.

REFERENCES

1. Long, P. H., and Bliss, E. A.: J. A. M. A. 108: 32, 1937.
2. Marshall, E. K., Jr., Emerson, K., Jr., and Cutting, W. C.: J. A. M. A. 108: 953, 1937.

*A small group of patients with acute pyelitis caused by the colon bacillus have been treated with prontylin, but sufficient time has not elapsed for us to draw conclusions as to its effectiveness.

3. Colebrook, L., and Kenney, M.: Lancet 1: 1279, 1936.
4. Schwentker, F. F., Gelman, S., and Long, P. H.: J. A. M. A. 108: 1407, 1937.

CASE REPORTS

GLOSSARY OF ABBREVIATIONS USED IN ABSTRACTS OF CASES

PABS: 0.8 per cent para-aminobenzenesulfonamide in physiologic salt solution.
Prontosil: 2.5 per cent aqueous solution (Winthrop).
Prontylin: Tablet containing 0.3 gm. para-aminobenzenesulfonamide.
i.m.: intramuscularly.
s.c.: subcutaneously.
i.v.: intravenously.
i.s.: intraspinally.
p.o.: by mouth.
Temperature: Highest reading of day, degrees F.

Case 1. H. L. *Diagnosis:* Meningitis and Meningococcemia. *Organism:* Meningococcus.

Male, aged eleven years, weight 72 pounds. Treatment begun twenty-four hours after onset. PABS i.s. 30 c.c. first day, 10 c.c. second and third days; s.c. 600 c.c. first day, 300 c.c. second, third, and fourth days. Temperature normal in twenty-four hours. Organisms disappeared in eighteen hours. Reaction: cyanosis, headache. *Recovery.*

Case 2. E. M. *Diagnosis:* Meningitis. *Organism:* Meningococcus.

Male, aged nineteen months, weight 26 pounds. Treatment begun five days after onset. PABS s.c. 50 c.c. first day; prontylin 2 gm. p.o. daily for seven days. Organisms disappeared in twenty-four hours. Temperature normal in twenty-four hours. Reaction: none. *Recovery.*

Case 3. J. C. *Diagnosis:* Meningitis and Meningococcemia. *Organism:* Meningococcus.

Male, aged nineteen months, weight 22 pounds. Treatment begun three days after onset. PABS i.v. 200 c.c. first, second, and third days; prontylin p.o. 1 gm. daily fourth to seventh day, 0.6 gm. daily seventh to ninth day. Organism disappeared in twenty-four hours. Temperature 100 to 101 eight days. Reaction: cyanosis, fever. *Recovery.*

Case 4. L. S. *Diagnosis:* Meningitis and Meningococcemia. *Organism:* Meningococcus.

Male, aged five years, weight 42 pounds. Treatment begun thirty-six hours after onset. PABS i.v. 500 c.c. first day, 600 c.c. second and third day, 300 c.c. fourth and fifth day; prontylin p.o. 2 gm. daily sixth to tenth day. Temperature 100 to 101 during therapy. Organism disappeared in twenty-four hours. Reaction: cyanosis, fever, headache. *Recovery.*

Case 5. R. C. *Diagnosis:* Meningitis. *Organism:* Meningococcus.

Male, aged six months, weight 20 pounds. Treatment begun forty-eight hours after onset. PABS s.c. 200 c.c. first day; prontylin p.o. 1.5 gm. daily first to sixth day, 0.9 gm. daily sixth to ninth day. Temperature normal eighteen hours. Organisms disappeared in twenty-four hours. Reaction: cyanosis. *Recovery.*

Case 6. M. K. *Diagnosis:* Erysipelas* of face and neck; cervical adenitis. *Organism:* β Hemolytic streptococcus (throat).

Female, aged eleven years, weight 103 pounds. Treatment begun two days after onset. Prontylin p.o. 4 gm. first day, 2 gm. daily second and third day. Erysipelas disappeared in forty-eight hours. Cervical adenitis required incision and drainage ten days later. Reaction: cyanosis. *Recovery.*

*It is presumed that the erysipelas was due to the hemolytic streptococcus.

Case 7. B. B. *Diagnosis:* Erysipelas of face and neck.

Female, aged seven weeks, weight 9 pounds. Treatment begun twenty-four hours after onset. Prontylin p.o. 2 gm. first day; prontosil i.m. 30 c.c. first day, 40 c.c. second day, 30 c.c. daily third and fourth days. Erysipelas disappeared in thirty-six hours. Reaction: cyanosis, acidosis. *Recovery.*

Case 8. R. Z. *Diagnosis:* Erysipelas and first degree burn of leg.

Male, aged eighteen months, weight 28 pounds. Treatment begun forty-eight hours after onset. Prontosil i.m. 30 c.c. first day, 20 c.c. daily second, third, and fourth days. Prontylin p. o. 0.9 gm. daily second to sixth day. Temperature normal third day. Erysipelas disappeared third day. Burn healed by sixth day. Reaction: none. *Recovery.*

Case 9. L. P. *Diagnosis:* Erysipelas of leg.

Female, aged eight years, weight 83 pounds. Treatment begun thirty-six hours after onset. Prontylin p.o. 6 gm. daily first to fourth day, 4 gm. daily fourth to eighth day, 2 gm. daily eighth to fifteenth day. Temperature normal on fourth day. Erysipelas disappeared on third day. Reaction: cyanosis. *Recovery.*

Case 10. R. F. *Diagnosis:* Erysipelas of back.

Male, aged two months, weight 9 pounds. Treatment begun twenty-four hours after onset. Prontylin p.o. 1.3 gm. first day, 0.6 gm. daily second to tenth day. Temperature normal in twelve hours. Erysipelas disappeared on third day. Reaction: none. *Recovery.*

Case 11. J. L. *Diagnosis:* Erysipelas of face, neck, and shoulder.

Female, aged one month, weight 8 pounds. Treatment begun twenty-four hours after onset. Prontylin p.o. 1.3 gm. first day, 1 gm. daily second and third days, 0.6 gm. daily fourth to eighth day. Temperature normal in thirty-six hours. Erysipelas disappeared in thirty-six hours. Reaction: cyanosis. *Recovery.*

Case 12. G. W. *Diagnosis:* Erysipelas of face.

Male, aged four months, weight 12 pounds. Treatment begun thirty-six hours after onset. Prontylin p.o. 1.6 gm. first day, 0.6 gm. daily second to fourth day, 0.4 gm. daily fourth to ninth day. Temperature normal in twenty-four hours. Erysipelas disappeared in thirty-six hours. Reaction: cyanosis. *Recovery.*

Case 13. J. C. *Diagnosis:* Erysipelas of abdomen and buttocks; cellulitis of penis and scrotum; septicemia. *Organism:* β Hemolytic streptococcus.

Male, aged three days, weight 7 pounds. Treatment begun twenty-four hours after onset. PABS i.v. 50 c.c. daily first to seventh day; prontylin p.o. 1.3 gm. first day, 0.6 gm. daily second to sixth day, 0.4 gm. daily sixth to twelfth day. Blood culture positive throughout course. Temperature 100 to 104. Reaction: cyanosis, jaundice. *Died.*

Case 14. G. P. *Diagnosis:* Erysipelas of face; congenital heart disease.

Male, aged nine days, weight 6 pounds. Treatment begun twelve hours after onset. Prontylin p.o. 1 gm. first day, 0.6 gm. daily second and third days. Temperature not elevated. No spread of erysipelas after prontylin begun. Reaction: cyanosis. *Died* third day, presumably of congenital heart lesion. Necropsy not done.

Case 15. J. D. *Diagnosis:* Peritonitis. *Organism:* β Hemolytic streptococcus.

Male, aged two months, weight 11 pounds. Treatment begun two days after onset. Prontosil i.m. 25 c.c. first day. Incision and drainage of abdomen done at admission. *Died* eighteen hours after operation.

Case 16. S. F. *Diagnosis:* Peritonitis. *Organism:* β Hemolytic streptococcus.

Female; aged sixteen months, weight 26 pounds. Treatment begun 1 week after onset. Prontosil i.m. 20 c.c. daily first and second days, 30 c.c. third day. Incision

and drainage of abdomen done at admission. Temperature 102 to 105 throughout course. *Died* third day after operation.

Case 17. P. A. *Diagnosis:* Peritonitis. *Organism:* β Hemolytic streptococcus.

Female, aged ten years, weight 75 pounds. Treatment begun three days after onset. Prontosil i.m. 60 c.c. daily first to sixth day; prontylin p.o. 1.6 gm. daily sixth to ninth day; PABS s.c. 150 c.c. daily first and second day, 300 c.c. daily second to seventh day. Temperature 100 to 104 throughout course. Incision and drainage of abdomen on second day. Blood transfusion second, third, sixth, and seventh days. Developed bilateral pneumonia and pericarditis on sixth day. Reaction: cyanosis. *Died* tenth day after operation.

Case 18. D. S. *Diagnosis:* Peritonitis; liver abscess. *Organism:* β Hemolytic streptococcus.

Male, aged three and one-half years, weight 34 pounds. Treatment begun seventeen days after onset. Prontosil i.m. 60 c.c. on seventeenth day; prontylin p.o. 4 gm. daily seventeenth to twenty-third day, 2 gm. daily twenty-third to twenty-ninth day. Incision and drainage of liver abscess on ninth day. Seven blood transfusions between tenth and twenty-fifth days. Reaction: cyanosis. *Died* on twentieth day after operation.

Case 19. E. M. *Diagnosis:* Vulvovaginitis. *Organism:* Gonococcus.

Female, aged three years, weight 34 pounds. Treatment begun five days after onset. Prontylin p.o. 2.6 gm. first day, 1.3 gm. daily second to fifth day. Organisms and vaginal discharge disappeared on third day. No recurrence after three months. Reaction: cyanosis. *Recovery.*

Case 20. M. Z. *Diagnosis:* Vulvovaginitis. *Organism:* Gonococcus.

Female, aged seven years, weight 45 pounds. Treatment begun three weeks after onset. Prontylin p.o. 6 gm. first day, 3 gm. daily second to eighth day, 4 gm. daily eighth to twenty-fourth day. Organisms and discharge disappeared on fifth day, recurred on ninth day, and were still present after three weeks. Blood PABS third day 5 mg. per cent. Blood PABS twelfth day 10 mg. per cent. Reaction: cyanosis. *Unimproved.*

Case 21. N. G. *Diagnosis:* Mastoiditis; sterile meningitis. *Organism:* β Hemolytic streptococcus.

Male, aged six years, weight 40 pounds. Treatment begun two weeks after onset. Prontosil i.m. 40 c.c. fifth day, 18 c.c., sixth day, 3 c.c. seventh day; prontylin p.o. 2 gm. sixth day, 0.6 gm. seventh day. Signs of meningitis appeared three days after bilateral simple mastoidectomy. All cultures of cerebrospinal fluid sterile. Temperature normal in eighteen hours. Reaction: cyanosis. *Recovery.*

Case 22. D. S. *Diagnosis:* Mastoiditis; sterile meningitis. *Organism:* β Hemolytic streptococcus.

Female, aged seven years, weight 60 pounds. Treatment begun three days after onset. PABS s.c. 300 c.c. daily first to fourth day; prontosil i.m. 30 c.c. daily second and third days; prontylin p.o. 2.6 gm. daily fifth to twentieth day. Left mastoidectomy two weeks before admission. Signs of meningitis appeared three days before admission. All cultures of cerebrospinal fluid sterile. Secondary left mastoidectomy day after admission. Temperature normal in four days. Reaction: cyanosis. *Recovery.*

Case 23. P. M. *Diagnosis:* Meningitis; mastoiditis. *Organism:* β Hemolytic streptococcus.

Female, aged five years, weight 35 pounds. Treatment begun two days after onset. PABS s.c. 250 c.c. first day, 550 c.c. second day, i.s. 30 c.c. first and third days; prontylin p.o. 1 gm. second day, 2.6 gm. daily third to sixth day, 1.3 gm.

daily sixth to twelfth day. Temperature normal in four days. Organisms disappeared in twenty-four hours. Reaction: cyanosis. *Recovery.*

Case 24. K. M. *Diagnosis:* Meningitis; mastoiditis. *Organism:* β Hemolytic streptococcus.

Male, aged eight years, weight 51 pounds. Treatment begun four days after onset. PABS s.c. 500 c.c. first day; 200 c.c. second day; i.s. 60 c.c. first day; prontylin p.o. 4 gm. daily first to eighth day. Signs of meningitis appeared three weeks after right mastoidectomy. Temperature normal four days after therapy started. Organisms disappeared from cerebrospinal fluid in twenty-four hours. Reaction: cyanosis. *Recovery.*

Case 25. J. P. *Diagnosis:* Mastoiditis; lateral sinus thrombosis; septicemia. *Organism:* β Hemolytic streptococcus.

Male, aged three years, weight 28 pounds. Treatment begun ten days after onset. Prontosil i.m. 30 c.c. daily second to eighth day; prontylin p.o. 2 gm. first day, 2 gm. daily eighth to fifteenth day. Temperature normal thirteenth day. Organisms disappeared from blood in eleven days. Reaction: cyanosis. *Recovery.*

Case 26. R. M. *Diagnosis:* Mastoiditis; peri-sinus abscess. *Organism:* β Hemolytic streptococcus.

Female, aged seven years, weight 47 pounds. Treatment begun three days after onset. Prontosil i.m. 35 c.c. first day, 42 c.c. second day, 7 c.c. third day; prontylin p.o. 2 gm. third day, one gm. fourth day. Temperature normal in two days. Reaction: cyanosis. *Recovery.*

Case 27. C. M. *Diagnosis:* Acute otitis media; mastoiditis. *Organism:* β Hemolytic streptococcus.

Female, aged four years, weight 30 pounds. Treatment begun eleven days after onset. Prontylin p.o. 2 gm. daily first to eighth day. No change in aural discharge after seven days of prontylin. Left simple mastoidectomy one month after admission. Reaction: none. *Unimproved.*

Case 28. E. G. *Diagnosis:* Acute otitis media; mastoiditis; scarlet fever. *Organism:* β Hemolytic streptococcus.

Female, aged six years, weight 37 pounds. Treatment begun three days after onset. Prontylin p.o. 4 gm. first day, 2.6 gm. daily second to eighteenth day. Organisms disappeared from aural discharge after twelve days of prontylin but x-ray films showed mastoiditis, and left simple mastoidectomy done eighteen days after admission. Hemolytic streptococcus cultured from mastoid. Reaction: cyanosis. *Unimproved.*

Case 29. L. P. *Diagnosis:* Acute otitis media. *Organism:* β Hemolytic streptococcus.

Male, aged five years, weight 42 pounds. Treatment begun one week after onset. Prontylin p.o. 4.3 gm. first day, 4 gm. daily second to fifth day, 2 gm. daily fifth to tenth day. Temperature normal in three days. Aural discharge disappeared in four days. Reaction: cyanosis, headache. *Improved.*

Case 30. G. A. *Diagnosis:* Acute otitis media. *Organism:* β Hemolytic streptococcus.

Male, aged ten years, weight 48 pounds. Treatment begun ten days after onset. Prontylin p.o. 4.6 gm. first day, 4 gm. daily second to fourth day, 1.3 gm. daily fourth to eighth day. Temperature normal in two days. Aural discharge disappeared in six days. Reaction: cyanosis. *Improved.*

Case 31. H. M. *Diagnosis:* Acute otitis media. *Organism:* β Hemolytic streptococcus.

Female, aged six years, weight 44 pounds. Treatment begun six days after onset. Prontylin p.o. 3 gm. first day, 2 gm. daily second to eighth day. Tempera-

ture normal in twenty-four hours. Aural discharge disappeared seven days. Reaction: cyanosis. *Improved.*

Case 32. V. D. *Diagnosis:* Acute otitis media; rubella. *Organism:* β Hemolytic streptococcus.

Female, aged five years, weight 40 pounds. Treatment begun one week after onset. Prontylin p.o. 2.3 gm. first day, 1.3 gm. daily second to ninth day. Temperature normal in two days. Left aural discharge disappeared in five days; right aural discharge disappeared in three weeks. Reaction: cyanosis. *Unimproved.*

Case 33. M. A. *Diagnosis:* Acute otitis media. *Organism:* β Hemolytic streptococcus.

Female, aged eight years, weight 47 pounds. Treatment begun three days after onset. Prontylin p.o. 2 gm. first day, 1.3 gm. daily second to seventh day. Temperature normal in two days. Bilateral aural discharge continued for six weeks. Reaction: cyanosis. *Unimproved.*

Case 34. U. R. *Diagnosis:* Acute otitis media. *Organism:* β Hemolytic streptococcus.

Male, aged seven years, weight 45 pounds. Treatment begun three days after onset. Prontylin p.o. 2 gm. daily second to fifth day. Temperature normal in twenty-four hours. Bilateral aural discharge remained for two weeks. Reaction: none. *Unimproved.*

Case 35. S. M. *Diagnosis:* Septicemia; acute arthritis. *Organism:* β Hemolytic streptococcus.

Female, aged one year, weight 12 pounds. Treatment begun ten days after onset. Prontosil i.m. 12 c.c. daily first to fourth day, 6 c.c. daily fourth to seventh day, 12 c.c. daily seventh to thirteenth day; prontylin p.o. 0.6 gm. daily thirteenth to seventy-eighth day. Septicemia and septic right elbow noted at same time. Septic left hip noted two weeks later. Blood culture sterile nine days after therapy begun. Temperature remained elevated two weeks after therapy begun. Reaction: cyanosis. *Recovery.*

Case 36. L. W. *Diagnosis:* Septicemia; acute arthritis. *Organism:* β Hemolytic streptococcus.

Female, aged three years, weight 35 pounds. Treatment begun one week after onset. Prontylin p.o. 4 gm. first day, 2.6 gm. second day, 4 gm. daily third to thirteenth day, 2 gm. daily thirteenth to twenty-second day. Temperature normal in five days. Organisms disappeared from blood stream in twenty-four hours. Arthritis disappeared after three weeks of therapy. Reaction: cyanosis. *Recovery.*

Case 37. M. C. *Diagnosis:* Septicemia; acute otitis media. *Organism:* β Hemolytic streptococcus.

Female, aged nine years, weight 48 pounds. Treatment begun five days after onset. Prontylin p.o. 6 gm. first day, 5 gm. daily second to ninth day, 3 gm. daily ninth to sixteenth day. Temperature normal in two days. Organisms disappeared from blood stream in twenty-four hours. Bilateral aural discharge disappeared in six days. Reaction: cyanosis, anemia, acidosis. *Recovery.*

Case 38. C. H. *Diagnosis:* Septicemia; wringer arm. *Organism:* β Hemolytic streptococcus.

Male, aged three years, weight 31 pounds. Treatment begun three days after onset. Prontosil i.m. 60 c.c. daily first, second and third days; prontylin p.o. 4 gm. daily first, second and third days, 6 gm. fourth day. Temperature normal in two days. Organisms disappeared from blood stream in twenty-four hours. Plastic operation to arm two weeks later. Reaction: cyanosis. *Recovery.*

REPORT OF PATIENTS TREATED WITH SULFANILAMIDE AT THE ST. LOUIS CHILDREN'S HOSPITAL

JACK BASMAN, M.D., AND ANNE M. PERLEY, M.A.
ST. LOUIS, MO.

SELECTED cases in the St. Louis Children's Hospital have been treated with sulfanilamide since December, 1936, following the report by Long and Bliss before the last meeting of the Southern Medical Association. For the most part the cases were selected for this new therapy by Dr. A. F. Hartmann or Dr. J. V. Cooke, whose advice and assistance in making this study and report have been greatly appreciated. We wish to thank both the Winthrop Chemical Company, Inc., and Merck and Co., Inc. for their generous supply of sulfanilamide. We also wish to thank Dr. W. B. Wendel for his assistance in helping us follow methemoglobin concentrations.

The material may be presented as follows: (97 cases)

I. Meningitis and brain abscess:
   1. Streptococcus, 1 (recovered)
   2. Meningococcus, 2 (recovered)
   3. Proteus, 1 (recovered)
   4. Pneumococcus, 3 (1 recovered—2 died)
   5. Influenza, 1 (died)
   6. Brain abscess:
      a. Pneumococcus, 1 (died)
      b. Streptococcus, 1 (recovered)

II. Acute upper respiratory tract infection:
   1. Lateral sinus phlebitis secondary to otitis media and mastoiditis, 1 (recovered)
   2. Otitis media and mastoiditis, 15 (recovered)
   3. Otitis media without definite mastoiditis, 9 (recovered)
   4. Tonsillitis, pharyngitis, rhinitis without otitis media, 15 (recovered)

III. Pneumonia: 1 (recovered)

IV. Empyema: 4 (2 recovered—2 died)

V. Peritonitis: 2 (1 recovered)

VI. Pyelitis: 2 (recovered)

VII. Erysipelas: 9 (recovered)

VIII. Cellulitis and erysipeloid: 4 (recovered)

IX. Osteomyelitis: 2 (1 recovered)

X. Septicemia without obvious portal of entry:
   1. Staphylococcus, 1 (died)
   2. Streptococcus, 1 (recovered)
   3. Pneumococcus, 1 (recovered)

XI. Rheumatic fever: 2 (1 recovered)

XII. Scarlet fever: 10 (recovered)

XIII. Miscellaneous: 9 (recovered)

From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

I. CASES OF MENINGITIS AND BRAIN ABSCESS

Our experience with meningitis has more than anything else contributed to a strong feeling on our part that sulfanilamide offers something in the treatment of severe infections which no other treatment heretofore recommended has ever accomplished. The following protocols of cases of meningitis and brain abscess treated by this new method should in themselves indicate why we regard sulfanilamide treatment in this light.

1. Streptococcus Meningitis

CASE 1.—L. W., a twenty-month-old male infant, weighing 10.4 kilograms, was admitted on Dec. 12, 1936, with a temperature of 41.3° C., due to a hemolytic streptococcus septicemia. The portal of entry may have been the upper respiratory tract, since this child had had an upper respiratory infection for the previous week. In addition to this infection, there was cellulitis of the left leg and symptoms interpreted as being due to meningismus, since the fluid from a lumbar puncture done shortly after admittance contained only six cells and proved to be sterile. This patient was selected as a good test case for sulfanilamide therapy, and we decided first to note the general trend of the infection before giving sulfanilamide (prontosil). For five days the child was followed with no treatment except proper feedings, fluid administration, and the application of hot wet dressings to the area of cellulitis. During this period his progress seemed favorable. The cellulitis localized and the fever tended to decline, averaging 38.6° C. on the fifth day in contrast to an average of 39.6° C. on the first two days after admittance. During the interval, however, an area of redness and swelling appeared over the first metacarpophalangeal joint of the fourth finger of the right hand. During this interval also the blood culture remained positive except on the fourth day after admittance. On the sixth day there was a sudden and unexpected rise in the temperature to 40.6° C. It was then felt that sulfanilamide therapy should be given a trial. A preliminary blood culture was taken, which subsequently proved to be positive for hemolytic streptococcus, and in spite of the absence of any meningeal signs, a lumbar puncture was done to rule out the onset of meningitis as a cause for the unexpected fever. This tap revealed cloudy spinal fluid with 4,500 cells of which 81 per cent were polymorphonuclear leucocytes. Streptococci were seen in the centrifuged and stained sediment and grown on culture media. They proved later to be the hemolytic type.

Sulfanilamide therapy in the form of prontosil intramuscularly was instituted the following day, Dec. 18, 1936, together with continuous spinal fluid drainage by means of a needle strapped in the lumbar spine and the continuous intravenous administration of fluid containing equal amounts of 10 per cent dextrose and lactate-Ringer's solution. Following institution of this treatment the temperature fell rapidly and came to normal in three days. Both the blood and spinal fluid cultures were sterile the day following the institution of treatment and remained so. The metastatic focus on the right hand disappeared spontaneously, and the area of cellulitis subsided to such an extent that we felt that it would eventually disappear. The continuous spinal and intravenous fluid administrations were continued for three days. At no time was the spinal fluid discolored pink. Eleven days after the institution of sulfanilamide therapy a soft fluctuant area developed at the site of the original cellulitis which when aspirated revealed thick pus from which the hemolytic streptococcus was cultured. This area was not red or tender and looked like a cold abscess. The subsequent convalescence was uneventful.

The sulfanilamide therapy in this case was the administration of prontosil intramuscularly, 10 c.c. every six hours for six doses. This was followed by 5 c.c.

every six hours for six doses. In addition, 0.16 gm. of sulfanilamide in the form of prontylin was given orally five times daily for seven days following the discontinuation of the intramuscular prontosil therapy.

This was our first case treated with sulfanilamide (prontosil and prontylin), and was also the first case of streptococcus meningitis in the St. Louis Children's Hospital to make a complete recovery, in which organisms were actually cultured from the spinal fluid.

TABLE I

DATE	SPINAL FLUID		BLOOD CULTURE	SULFANILAMIDE	REMARKS
	CELL COUNT	CULTURE			
12/12/36	6	Negative	Hemolytic streptococcus		
12/14/36			Hemolytic streptococcus		
12/15/36			Negative		
12/16/36			Hemolytic streptococcus		
12/17/36			Hemolytic streptococcus		
12/18/36	4,500	Hemolytic streptococcus	Negative	10 c.c. prontosil I.M.* 10 c.c. prontosil I.M.	
12/19/36		Negative	Negative	10 c.c. prontosil I.M. 10 c.c. prontosil I.M. 10 c.c. prontosil I.M.	
12/20/36			Negative	10 c.c. prontosil I.M.	
12/22/36	41	Negative	Negative	12/21/36: 5 c.c. prontosil I.M. 5 c.c. prontosil I.M. 5 c.c. prontosil I.M. 5 c.c. prontosil I.M.	Sulfanilamide 0.16 gm. every 4 hr. by mouth. Discontinued 12/29/36.
12/23/36			Negative	12/22/36: 5 c.c. prontosil I.M. 5 c.c. prontosil I.M.	
12/25/36			Negative		
12/30/36	24	Negative			

*I.M. = Intramuscularly.

2. Meningococcus Meningitis

Since sulfanilamide therapy was instituted in the St. Louis Children's Hospital, two children with meningococcus meningitis have been admitted.

CASE 1.—E. M., a male infant of eighteen months, weighing 12 kilograms, showed classical signs of meningitis, which according to the history had been present for five days. The initial spinal tap showed cloudy fluid containing 2,250 polymorphonuclear leucocytes per cubic millimeter. Meningococci were seen in the stained sediment, and subsequently grown on culture. Immediately after this tap, 15 c.c. of antimeningococcus serum were given intrathecally and intramuscularly. A blood culture taken at this time was sterile. Two hours after admittance to the hospital, sulfanilamide therapy was instituted, and no more serum given. During the first eighteen hours of the first day of sulfanilamide therapy, 2.6 gm. of sulfanilamide were given in the form of a 0.85 per cent solution; 15 c.c. being given intrathecally and 85 c.c. subcutaneously, repeated twice. During the second and third days of sulfanilamide therapy a total of 1.7 gm. were given daily in the same manner, in two doses. On the fourth day of sulfanilamide therapy, 0.8 gm. was given by the combined intraspinal and intramuscular routes. Following the parenteral ad-

ministration of sulfanilamide, 0.16 gm. was given by mouth every four hours, together with 10 c.c. of molar sodium *r*-lactate, for six doses for eight days. The fever began to decline on the fourth day following institution of therapy, and was normal after the fifth day. The spinal fluid ten hours after the beginning of sulfanilamide therapy still showed meningococci on culture. The fluid secured eighteen hours after the institution of therapy proved to be sterile, and all subsequent taps showed sterile fluid. From Table II the behavior of the cell count may be noted. Otitis media probably contributed to the fever in this case, and after bilateral myringotomy on the third day of treatment the temperature fell abruptly. *Staphylococcus aureus* and the diphtheroid bacillus were cultured from the aural discharge. Except for the initial administration of antimeningococcus serum, no other treatment was given to this child.

TABLE II

DATE	SPINAL FLUID		SULFANILAMIDE	REMARKS
	CELL COUNT	CULTURE		
5/2/37 11:00 P.M.	2,250	Meningococcus		15 c.c. meningococcus serum—intrathecally. Blood culture negative. 15 c.c. meningococcus serum intramuscularly. Smear: meningococcus.
5/3/37 1:00 A.M.			100 c.c. of 0.8% solution intrathecally and subcutaneously	
11:00 A.M.	4,075	Meningococcus	100 c.c. of 0.8% solution intrathecally and subcutaneously	2.6 gm.
7:00 P.M.	3,250	Negative	100 c.c. of 0.8% solution intrathecally and subcutaneously	
5/ 4/37	1,375	Negative	100 c.c. of 0.8% solution intrathecally and subcutaneously	
	850	Negative	100 c.c. of 0.8% solution intrathecally and subcutaneously	1.7 gm.
5/ 5/37	350	Negative	100 c.c. of 0.8% solution intrathecally and subcutaneously	
	300	Negative	100 c.c. of 0.8% solution intrathecally and subcutaneously	1.7 gm.
5/ 6/37	225	Negative	100 c.c. of 0.8% solution intrathecally and subcutaneously	0.85 gm. CO_2 cont. of blood serum 47.5 vol. per cent.
5/ 8/37	173	Negative	-	Sulfanilamide started, 0.16 gm. every 4 hr. by mouth 5/6/37. 10 c.c. Na lactate three times a day by mouth.
5/10/37	178	Negative	-	5/8/37 Sulfanilamide 0.33 gm. every 4 hr. by mouth until 5/15/37.
5/13/37	13	Negative	-	

CASE 2.—D. R., a four-year-old white boy, weighing 11 kilograms, was admitted to the hospital, unconscious, about twenty-four hours after the onset of meningeal symptoms, with classical signs of meningitis. The initial spinal tap showed turbid fluid with 12,000 polymorphonuclear leucocytes. Meningococci were found on smear and grown on culture. A blood culture taken at this time proved to be sterile.

TABLE III

DATE	SPINAL FLUID		SULFANILAMIDE				REMARKS
			ADMINISTRATION		MG. PER CENT CONCENTRATION‡		
	CELL COUNT	CULTURE	PARENTERALLY	ORALLY	BLOOD	SPINAL FLUID	
6/ 3/37	12,000	Meningococcus	1 gm. in 100 c.c. saline I.T.*—S.C.†	0.33 gm. every 4 hr.			Smear—meningococcus. Blood culture—negative.
6/ 4/37	7,000	Meningococcus	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.			
			1 gm. in 100 c.c. saline S.C.	0.33 gm. every 4 hr.			
	7,128	Negative	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.			
6/ 5/37	3,880	Negative	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.	4.2	3.6	
			1 gm. in 100 c.c. saline S.C.				
			1 gm. in 100 c.c. saline I.T.—S.C.				
6/ 6/37	748	Negative	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.			
	291	Negative	1 gm. in 100 c.c. saline S.C.				
			1 gm. in 100 c.c. saline I.T.—S.C.				
6/ 7/37	456	Negative	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.	7.7	10.0	11:30 A.M. 1 gm. in 100 c.c. saline S.C.
			1 gm. in 100 c.c. saline S.C.			11.0	
			1 gm. in 100 c.c. saline S.C.			9.6	1:30 P.M.
						11.4	2:30 P.M. Methemoglobin less
						11.1	3:30 P.M. than 5 per cent
							4:20 P.M. of total hemoglobin.
6/ 8/37	372	Negative	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.			
			1 gm. in 100 c.c. saline S.C.				
6/ 9/37	104	Negative	1 gm. in 100 c.c. saline I.T.—S.C.	0.33 gm. every 4 hr.		19.2	
			1 gm. in 100 c.c. saline S.C.				
6/10/37	–	–		0.33 gm. 3 times a day	1.0		
6/11/37	–	–	–	0.33 gm. 3 times a day			
6/12/37	–	–	–	(Discontinued)			
6/16/37					No color		

*I. T. = Intrathecally.

†S.C. = Subcutaneously.

‡Sulfanilamide determinations were carried out by the method described by E. K. Marshall, Jr., in the Proc. Soc. Exper. Biol. & Med. 36: 422, 1937.

Sulfanilamide therapy was instituted immediately, and no antimeningococcus serum or antitoxin given. The details of the treatment may be noted in Table III. In brief, 4 gm. were given daily for four days by the combined intrathecal, intramuscular, and oral routes. On the fifth and sixth days, 3 gm. were given daily by the same combination of routes, and for the next three days 0.33 gm. was given three times a day by mouth. The temperature in this case was never high, the maximum being 38.6° C. eight hours after admittance. It fell almost to normal after forty-eight hours, and then became somewhat more elevated until on the seventh day a temperature of 39.5° C. was reached. Because of the absence of physical signs to explain the fever at this time, and because of the clearing of the spinal fluid, it was felt that the fever might be due to sulfanilamide administration, which was accordingly discontinued. The temperature fell promptly to normal. As in the previous case, only the spinal fluid secured on the first tap following institution of treatment proved positive for organisms. In this case the second tap was nine hours after the institution of treatment. All subsequent samples of spinal fluid were sterile.

The clinical courses of these two cases of meningococcus meningitis compared favorably with any of our cases previously treated with either antimeningococcus serum or antitoxin.

3. B. Proteus Meningitis

CASE 1.—E. G., a nine-year-old girl, weighing 23 kilograms, was admitted to the hospital on May 31, 1937, with a history of fever, drowsiness, earache, and dizzy spells of four days' duration. Three years previously she had had scarlet fever, which resulted in chronic otitis media on the left side, a purulent ear discharge recurring particularly with upper respiratory tract infections.

A lumbar puncture made shortly after admittance showed cloudy fluid with 1,970 polymorphonuclear leucocytes per cubic millimeter. A gram negative, somewhat pleomorphic bacillus was seen on smear, which later, on culture, corresponded to *B. proteus*. A similar organism was obtained at this time on blood culture.

Sulfanilamide therapy was then carried out, as may be noted in Table IV. As in the previous case, sulfanilamide was administered intrathecally, intramuscularly, and orally, 0.3 gm. per kilogram of body weight being given the first day, 0.4 gm. the second day, and about 0.5 gm. on the third, fourth, and fifth days. The dose was then reduced to 0.3 gm. per kilogram of body weight on the sixth and seventh days, and to 0.2 gm. per kilogram on the eighth and ninth days. For three days following the institution of therapy, the child seemed somewhat better, the temperature falling gradually from 40.5° C. to 38.2° C. During this interval the child not only continued to look better, but both the blood and spinal fluid became sterile, the latter, as in the preceding case, showing a growth only on the first tap following institution of treatment. On the fourth day, however, the temperature rose sharply to 40.8° C., and the child looked worse, and more meningeal, despite the failure of the spinal fluid to show any increase in the cells or to show organisms. Mastoidectomy was performed the following day because of a continuation of the elevated temperature. A conlescent type of mastoiditis was found, with cells filled with pus, granulation tissue, and necrotic débris. The lateral sinus was covered with granulation tissue, but was not thrombosed. An area of the dura was exposed over the middle fossa, but did not look very abnormal. The tegmen antra and tegmen tympani were very soft, as was also the bone behind the region of the labyrinth, and also in Trautman's triangle. In removing the necrotic bone a large amount of dura was exposed medial to the internal meatus. Culture from the mastoid grew *B. proteus*. Following operation the temperature began to subside, and in five days was normal, and convalescence was uneventful, except for two transient periods of fever, each following transfusions on the twelfth and thirteenth days after admittance.

TABLE IV

DATE	SPINAL FLUID		SULFANILAMIDE				REMARKS
			ADMINISTRATION		MG. PER CENT CONCENTRATION		
	CELL COUNT	CULTURE	PARENTERALLY	ORALLY	BLOOD	SPINAL FLUID	
5/31/37							
9 A.M.	1,971	*B. proteus*	2 gm. in 200 c.c. saline I.T.*—S.C.†	3.0 gm.			Blood culture—*B. proteus.*
7 P.M.	2,450	*B. proteus*	2 gm. in 200 c.c. saline I.T.—S.C.				
6/ 1/37							
9 A.M.	600	Negative	2 gm. in 200 c.c. saline I.T.—S.C.	3.0 gm.	3.0	3.0	
4 P.M.	–	Negative	4 gm. in 400 c.c. saline I.T.—S.C.				
6/ 2/37	650	Negative	4 gm. in 400 c.c. saline I.T.—S.C.	3.0 gm.			Blood culture—negative.
	370	Negative	4 gm. in 400 c.c. saline I.T.—S.C.				
6/ 3/37	367	Negative	4 gm. in 400 c.c. saline I.T.—S.C.	3.0 gm.	7.7	7.3	Queckenstedt test negative.
			4 gm. in 400 c.c. saline I.T.—S.C.				Citrated blood 250 c.c. I.V.
6/ 4/37	90	Negative	4 gm. in 400 c.c. saline I.T.—S.C.	3.0 gm.			Mastoidectomy.
			4 gm. in 400 c.c. saline I.T.—S.C.				Citrated blood 250 c.c. I.V.
6/ 5/37	125	Negative	2 gm. in 200 c.c. saline I.T.—S.C.	3.0 gm.	6.1	14.5	Blood culture—negative.
			2 gm. in 200 c.c. saline S.C.				
6/ 6/37	225	Negative	2 gm. in 200 c.c. saline I.T.—S.C.	3.0 gm.			
			2 gm. in 200 c.c. saline S.C.				
6/ 7/37	76	Negative	1 gm. in 100 c.c. saline S.C.	3.0 gm.	9.8		Methemoglobin between 10 and 15 per cent of total hemoglobin.
			1 gm. in 100 c.c. saline S.C.				
6/ 8/37	121	Negative	1 gm. in 100 c.c. saline S.C.		3.1		
6/10/37					3.1		Sulfanilamide by mouth discontinued.

*I.T. = Intrathecally.
†S.C. = Subcutaneously.

4. Pneumococcus Meningitis

CASE 1.—P. H., a girl of nine years, weighing 23 kilograms, was admitted to the hospital on April 25, 1937, with classical signs of meningitis of three days' duration. It was felt that the left mastoid was the probable portal of entry, because of the history of a discharging left ear for the previous two years. The mastoid on this side had been operated upon twice previously. Stenosis of the external canal had developed which made an examination of the drumhead impossible. Spinal fluid obtained shortly after admittance was cloudy, showing 2,000 polymorphonuclear leucocytes per cubic millimeter. A few cocci, staining indeterminately by the Gram method, were seen in the sediment. Because of the possibility of the presence of meningococcic meningitis, 50,000 units of meningococcus antitoxin were given intravenously, and 15 c.c. of antimeningococcus serum were given intramuscularly. In addition, however, sulfanilamide therapy was instituted, and the details of administration may be seen in Table V. Later, on culture, the organism was found to be Type V pneumococcus. In addition to the initial spinal fluid, three different samples on April 26, two on April 27, and one on April 28 showed the same organism on culture. The first sterile fluid was secured on April 29. At this time the cell count was 400. By this time the temperature had fallen almost to normal, averaging between 37° and 38° C. on April 29. At this time parenteral administration of sulfanilamide was discontinued, but 4.0 gm., however, were given daily by mouth in six doses of ten grains each. Spinal fluid on May 1 showed only 80 cells, and proved to be sterile. On May 2, however, despite the fact that the cell count was only 48, organisms (Type V pneumococcus) grew on culture. The next day the cell count was 6,000, and the culture still positive. Sulfanilamide therapy was then resumed orally, intrathecally, and intramuscularly, as may be noted from Table V, following which the spinal fluid again became sterile, with a steadily diminishing cell count. The oral administration of sulfanilamide was continued in doses of four grams daily. The temperature remained slightly elevated, but we were reluctant to discontinue the sulfanilamide therapy to note whether or not the temperature would fall as a result, because of the previous exacerbation of symptoms which followed reduction in dosage. It was finally decided to continue sulfanilamide therapy until the mastoid could be cleaned out. This was done five weeks after admittance, on May 30, 1937. Necrotic infected cells were noted, together with a large area of dura covered with granulation tissue. The drumhead quite unexpectedly was found to be without perforation and practically normal. Sulfanilamide was continued until June 14. Convalescence was uneventful except for an occasional transient rise in temperature unexplained by any of our findings. At the present time the patient is at the country convalescent home and doing well. This case was the first case of pneumococcus meningitis proved by culture to recover in the St. Louis Children's Hospital.

CASE 2.—J. B., a girl of eight years, weighing approximately 25 kilograms, was admitted on April 15, 1937, with symptoms of meningitis of about twenty-four hours' duration. In addition there was discharge from the right ear, the otitis media having begun two weeks previously, and tenderness over the right mastoid. Lumbar puncture shortly after admittance showed turbid spinal fluid containing 6,800 polymorphonuclear leucocytes per cubic millimeter. No organisms were seen on direct smear, but on culture a Type III pneumococcus was grown. A Queckenstedt test at this time was negative. A simple right mastoidectomy was performed on the night of admittance, the mastoid cells being necrotic with some granulation tissue. The lateral sinus appeared more gray than normal, but was not thrombosed. That same evening the child was given 50,000 units of meningococcus antitoxin (this was before the identity of the organism was ascertained), and on the following day, 10 c.c. of prontosil were given intramuscularly three times a day,

TABLE V

DATE	SPINAL FLUID		SULFANILAMIDE				REMARKS
			ADMINISTRATION		CONCENTRATION		
	COUNT	CULTURE	PARENTERALLY	ORALLY	BLOOD MG. PER CENT	SPINAL FLUID, MG. PER CENT	
4/25/37	2,000	Pneumococcus Type V		4.0 gm.			Blood culture negative. 50,000 U. meningococcus antitoxin I.V. 15 c.c. meningococcus serum I.T.
4/26/37	2,000	Positive	Prontosil 10 c.c. I.M.	4.0 gm.			
	1,500	Positive					
	1,500	Positive					
4/27/37	1,000	Positive	Prontosil 10 c.c. I.M.	4.0 gm.			First I.T. sulfanilamide.
	800		Prontosil 10 c.c. I.M.				
			Prontosil 10 c.c. I.M.				
			1 gm. in 100 c.c. saline I.T.—S.C.				
4/28/37	780	Positive	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.			Queckenstedt test negative.
			1.6 gm. in 200 c.c. saline I.T.—S.C.				
			Prontosil 10 c.c. I.M.				
			Prontosil 10 c.c. I.M.				
4/29/37	400	Negative	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.			4 gm. given daily by mouth. No lumbar puncture was done from 4/29 to 5/1/37.
			1.6 gm. in 200 c.c. saline I.T.—S.C.				
5/ 1/37	80	Negative		4.0 gm.			
5/ 2/37	48	Positive		4.0 gm.			
5/ 3/37	6,000	Positive	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.			No parenteral administration of sulfanilamide from 4/29 to 5/3/37. Clinically worse.
5/ 4/37	6,000	Positive	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.			
5/ 5/37	273	Negative	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.			
5/ 7/37	170	Negative	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.			
5/ 8/37	225	Negative	1.6 gm. in 200 c.c. saline I.T.—S.C.	4.0 gm.	4.2		Citrated blood 250 c.c. I.V.
5/11/37	67	Negative		4.0 gm.			Citrated blood 250 c.c. I.V.
5/12/37	34	Negative		4.0 gm.			
5/16/37	50	Negative		4.0 gm.			
5/20/37	-	Negative		4.0 gm.	10.7		
5/21/37	-	Negative		4.0 gm.	11.5	9.6	
6/12/37	64	Negative		4.0 gm.			Oral administration discontinued 6/14/37.

I.T. = Intrathecally. I.M. = Intramuscularly.
S.C. = Subcutaneously. I.V. = Intravenously.

and sulfanilamide (prontylin) was given orally in doses of five grains every four hours. After a period of slight improvement, the course of the infection again became unfavorable. On April 18, 1937, a continuous spinal fluid drainage by the needle method was instituted, and on the same day a continuous intravenous drip was started. Despite a fall in cell count to 221 on April 20, 1937, the spinal fluid continued to show the Type III pneumococcus on culture, and the child died on the thirteenth day after admittance. In reviewing this case, it seems to us at the time of this writing that we should have given much more sulfanilamide than we did, and some also should have been given intrathecally.

CASE 3.—S. F., a twelve-year-old white female, was admitted to the hospital on April 13, 1937, with the history of an upper respiratory tract infection of two weeks' duration. One week prior to admittance she had what was diagnosed as a sinus infection, which was followed by fever, headache, vomiting, and a stiff neck. Upon admittance all the classical signs of meningitis were present. Lumbar puncture revealed cloudy spinal fluid with 1,340 cells per cubic millimeter, of which 95 per cent were polymorphonuclear leucocytes. Gram-positive diplococci were seen on smear and grown on culture. Her temperature on admittance was 38.5° C., and it was felt at the time that little could be offered as the meningitis was apparently of one week's duration. On the evening of admittance continuous spinal drainage by catheter, and intravenous drip were instituted. She was also given 10 c.c. of prontosil intramuscularly. She expired that evening, about fifteen hours after admittance. This patient died before adequate treatment was instituted.

5. Influenzal Meningitis

CASE 1.—R. B., a one-year-old white female, entered the hospital on May 27, 1937, with the history of an upper respiratory infection of three weeks' duration. For the past week there had been bilateral earache, and both tympanic membranes were opened one week before admittance; drainage was adequate. The day before admittance the child had a severe convulsion.

Physical examination revealed an acutely ill child who seemed rigid. The fontanel was closed. Both ear canals were clean, and the drums showed signs of healing. There were signs of meningeal irritation with positive Kernig's. A lumbar puncture revealed cloudy fluid with 80 per cent polymorphonuclear leucocytes. Short gram-negative bacilli were seen on smear. Blood culture grew *B. influenza*, as did the spinal fluid. Her weight was 5.4 kilograms. The child was given one gram of sulfanilamide every twelve hours by the combined subcutaneous and intraspinal routes. Intraspinal injection ranged between 10 and 15 c.c. The recommended dose of one-tenth gram per kilogram body weight was six-tenths gram, but in view of the overwhelming infection, the drug was given in larger doses to insure an adequate blood concentration. Her temperature on admittance was 38° C. The child expired the following day. The urine, Wassermann reaction, and tuberculin test were negative. Hemoglobin was 58 per cent, red blood cell count 2,380,000, white blood cell count 5,600 with a fairly marked shift to the left. On May 28, 1937, the sulfanilamide concentration of the blood was 11.8 mg. per cent, and of the spinal fluid, 9.0 mg. per cent. The temperature gradually rose to 41.3° C. on the second day of admittance when the child expired. In this case the infection was overwhelming. Sulfanilamide could not be given orally because of the child's moribund state.

6. Brain Abscess

CASE 1.—H. L., a four-year-old white male, was admitted to the hospital on May 5, 1937, with a history of vomiting and headache for six weeks. Three months prior to this time he had lobar pneumonia with empyema. The organism was not identified. There was also a suppurative bilateral otitis media, which had been draining up to

the time of admittance. Two weeks before admittance the child fell, striking his head; there were no convulsions or periods of unconsciousness. The temperature had been normal.

Upon physical examination the child did not appear acutely ill. Both fundi showed marked edema and choking, and there was a suggestive Babinski on the left. There was no facial weakness. Blood pressure was 90/68. A lumbar puncture on admittance showed 5 cells, and the Queckenstedt was negative. It was felt at the time that the child had a brain abscess and a ventriculogram was suggested, but permission for it was refused and he was signed out under protest.

The child was brought back into the hospital on May 19, 1937, because of increasing severity of symptoms. The ventriculogram was done, which showed a lesion in the left frontal lobe, displacing the ventricular system. An abscess was aspirated, and 30 c.c. of pus were obtained from which pneumococcus Type III was grown. On May 28, 1937, a lumbar puncture was done, revealing purulent fluid. This also grew pneumococcus Type III. A few days later the abscess was again entered and a drain inserted through a new opening. He was started on sulfanilamide on May 21, 1937, which was continued to the time of death on June 7, 1937. It was given intrathecally, intramuscularly, and subcutaneously throughout the entire course. His weight was 15 kilograms, and he was given a daily dose of 0.3 gm. of sulfanilamide per kilogram body weight by the combined oral, intrathecal, and intramuscular routes, for the first seven days following the aspiration of the brain abscess. From then on, until the time he expired, he was given sulfanilamide somewhat irregularly without any constant daily dose, the minimum being 0.4 gm. per kilogram body weight, and the maximum 0.6 gm. per kilogram body weight per day. Sulfanilamide concentration in the blood ranged from 1.2 mg. per cent to 6.0 mg. per cent. The abscess fluid concentration on May 26, 1937, was 1.5 mg. per cent, and the blood was 1.2 mg. per cent. Spinal fluid concentrations ranged from 3 to 6.9 mg. per cent. At no time were we able to get his sulfanilamide concentration to the desired 10 to 11 mg. per cent, although he was given as much as 0.6 gm. per kilogram body weight. Perhaps the sulfanilamide was swept out very rapidly from the blood stream because of a very large fluid intake and the marked diuresis which it created.

Case 2.—C. E., a twelve-year-old colored boy, was admitted to the hospital on Jan. 20, 1937, with a complaint of pain below the right eye, and a purulent nasal discharge of five weeks' duration. There had also been some projectile vomiting. The temperature was 37.2° C. There was swelling of the right eyelid and tenderness about the right frontal sinus. Both fundi were choked, and the retinal veins distended. The mucous membrane of the nose was thick, red, and encrusted. There was a suggestive bilateral Oppenheim and Babinski. A lumbar puncture done on Jan. 22, 1937, revealed 13 cells with a negative Pandy. A Queckenstedt at this time was within normal limits. An x-ray film of the paranasal sinuses showed haziness of the right frontal, and a stereoscopic x-ray picture of the skull showed prominent sutures which were slightly separated, and a defect of the right frontal bone, suggestive of osteomyelitis. On Jan. 23, 1937, he was given 10 c.c. of prontosil intramuscularly. At this time the right frontal and ethmoid sinuses were drained through an external approach. Both outer and inner tables were found to be necrotic, and a large subdural right frontal brain abscess was encountered which was draining inadequately through the nose. The following day 30 c.c. of prontosil were given intramuscularly. He was then started on sulfanilamide, 5 gr. every four hours, which was continued until discharge on February 22. The culture from the abscess and nasal discharge grew a nonhemolytic streptococcus. His temperature curve never was above 38.0° C. Following the operation the patient collapsed and was revived by intravenous acacia solution. His course in the hospital was uneventful, and he was sent home Feb. 22, 1937, and told to return at a later date. He again entered the

hospital on March 15, 1937, because of edema of the right eyelid for three weeks. At this time both fundi were normal. The sinus tract and the ethmoid were reopened, and he did extremely well from then on until discharge on April 3, 1937. No further sulfanilamide medication was instituted.

II. ACUTE UPPER RESPIRATORY TRACT INFECTION

1. Lateral Sinus Phlebitis Secondary to Otitis Media and Mastoiditis

CASE 1.—A. H., a three-year-old white girl, was admitted to the hospital on June 11, 1937. She entered because of a draining right ear and fever of eight weeks' duration, and pain in the right knee of one day's duration. At times the ear would stop draining for a day or two. The temperature had ranged between 104° and 105° F. for three or four days prior to admittance. There had been considerable loss of weight during the illness.

On physical examination the child looked acutely ill. The temperature was 38.4° C. She was pale and poorly developed. In addition to an acute nasopharyngitis, there was a foul-smelling purulent discharge from the right ear and some mastoid tenderness on that side. There was mild choking of both discs, more on the left than right. There was pain on motion of the right knee, which was somewhat swollen. Our impression at the time was that there existed right mastoiditis with thrombosis of the lateral sinus, septicemia, and a metastatic involvement of the right knee. A blood culture grew out a hemolytic streptococcus. A Queckenstedt suggested a partial block on the right side. She was immediately started on sulfanilamide therapy, and given one-tenth gram per kilogram of body weight per twenty-four hours by mouth, and one gram three times a day parenterally; she was also given 13 c.c. of molar sodium lactate four times daily. Her weight at this time was 13 kilograms. Blood cultures taken on June 12, 13, and 14 continued to be positive for the hemolytic streptococcus. A blood culture taken the morning of June 16 was negative. The Queckenstedt test repeated at this time indicated a complete block on the right side. On June 16 a right mastoidectomy was done, and the lateral sinus found to be gray and indurated. The right jugular vein was then ligated and the lateral sinus opened, pus being obtained from which hemolytic streptococcus grew. The blood culture taken the day following operation remained negative. On June 19, twelve hours before the lateral sinus was probed to secure better drainage, the blood culture became positive again; subsequent blood cultures, however, were negative. After the second day of treatment with sulfanilamide the temperature subsided rapidly, but did not become normal until three days after mastoidectomy. On the day of mastoidectomy, the daily dose of sulfanilamide was reduced to two grams parenterally, then reduced the following day to one gram. One week after admittance the daily oral administration was maintained at 2.0 gm. (Table VI). The urine continued to be alkaline to litmus from the onset of the administration of sodium lactate.

2. Otitis Media With Mastoiditis

Sulfanilamide therapy was used in fifteen cases with otitis media and mastoiditis. Thirteen were operated upon and two subsided without the necessity of operation. All recovered. It is extremely difficult to evaluate the rôle which sulfanilamide played in the recovery of these children. In a number of cases the drug was not administered until after operation, having been given with the idea of preventing any postoperative spread of infection. Perhaps the most outstanding feature in this group of cases is the smooth postoperative course with lack of com-

TABLE VI

DATE	SERUM			CONCENTRATION OF SULFANILAMIDE		ADMINISTRATION OF SULFANILAMIDE		OXYGEN CAPACITY VOL. PER CENT	HB. BY O_2 CAP. GM. PER CENT	HB. BY SAHLI GM. PER CENT	REACTION OF URINE TO LITMUS	BLOOD CULT.	CITRATED BLOOD I.V.†	REMARKS
	CO_2 CONT. VOL. PER CENT	SUGAR MG. PER CENT	LACTIC ACID MG. PER CENT	BLOOD MG. PER CENT	SPINAL FLUID MG. PER CENT	PARENTERALLY S.C.*	ORALLY							
6/11/37							3.5 gm.				Alkaline	Hemo. strep.		
6/12/37 11:20 A.M.				4.8	3.8	2.0 gm.	1.6 gm.				Alkaline	Hemo. strep.	100 c.c.	Queckenstedt suggestively positive.
6/13/37						3.0 gm.	1.6 gm.				Alkaline	Hemo. strep.	180 c.c.	
6/14/37						3.0 gm.	1.6 gm.						150 c.c.	
9:00 A.M.				4.9										
11:00 A.M.				10.3							Alkaline	Hemo. strep.		
6/15/37						3.0 gm.	1.3 gm.						130 c.c.	
9:00 A.M.				8.9							Alkaline	Hemo. strep.		1 gm. sulfanilamide. Queckenstedt positive.
10:00 A.M.				14.7										
11:30 A.M.				14.7										
12:30 P.M.				13.3										
2:00 P.M.				13.0										
4:00 P.M.				14.9	10.6									
6/16/37						2.0 gm.	2.0 gm.				Alkaline	Neg.	200 c.c.	Operation.
6/17/37	41.8	102.0	15.0	13.5		1.0 gm.	2.0 gm.	9.8	7.3	9.7	Alkaline	Neg.	240 c.c.	
6/18/37						-	2.0 gm.				Alkaline	Neg.	250 c.c.	
6/19/37	44.1		18.5	5.6		-	2.0 gm.	14.4	10.8	11.8	Alkaline	Pos.	200 c.c.	Bl. culture positive 12 hr. after sinus was probed.
6/20/37							2.0 gm.				Alkaline	Neg.	130 c.c.	
6/21/37	48.2		19.4	7.0			1.6 gm.	14.9	11.1	12.2	Alkaline	Neg.	250 c.c.	
6/22/37	44.8		20.7	6.1		-	-	18.1	13.5	14.5	Alkaline	Neg.	180 c.c.	

*S.C. = Subcutaneously.
†I.V. = Intravenously.

plications. The impression of most of the observers following these cases, however, was that definite clinical improvement followed the institution of sulfanilamide therapy.

3. Otitis Media Without Definite Mastoiditis

In the nine cases of otitis media without mastoiditis that were treated by sulfanilamide therapy, it is also extremely difficult to evaluate the results, since in most of these patients myringotomy had already been done by the time sulfanilamide was started. In a number of instances an elevated temperature dropped to normal limits the day following the myringotomy and sulfanilamide therapy. In a few patients the temperature was normal before sulfanilamide was started. None of these infections went on to mastoiditis.

4. Tonsillitis, Pharyngitis, and Rhinitis Without Otitis Media

In nine of these fifteen cases there was marked clinical improvement with some decrease in temperature when sulfanilamide was given in adequate doses. In the other six cases no conclusion can be drawn as the dosage was small, and the temperature had begun to subside before the drug was given.

III. PNEUMONIA

CASE 1.—C. R. entered the hospital on March 3, 1937, with signs of interstitial pneumonia and maxillary sinusitis. No hemolytic streptococci were grown from the throat or blood. The temperature tended to be remittent, fluctuating from 38° to 40° C. The child was started on sulfanilamide, 0.66 gm., three times a day, and it was given for ten days following admittance. The sixth day after admittance her temperature dropped to normal and remained there. Fifteen cubic centimeters of sodium lactate were given every four hours along with the sulfanilamide.

IV. EMPYEMA

CASE 1.—G. A., a thirteen-month-old white baby boy, entered the hospital on May 22, 1937, with the history of lobar pneumonia eight weeks prior to admittance. This was followed by empyema and an open drainage was done about three weeks before admittance. Two weeks later the tube was removed, but the wound continued to drain pus. The temperature was 38.8° C. Physical examination revealed a poorly developed white boy who appeared chronically ill. The expansion of the left chest was meager. There was a small draining sinus in the left posterior axillary line. The entire left side was dull to percussion, and breath sounds were faint. There was an absence of tactile and vocal fremitus. Fluoroscopy showed the heart pushed to the right, and the left chest filled with fluid. Both tympanic membranes were bulging and a bilateral myringotomy revealed pus that grew *Staphylococcus aureus*. The pus draining from the empyema sinus tract grew a hemolytic streptococcus. In view of this finding the child was put on sulfanilamide, 0.1 gm. per kilogram daily by mouth. His weight was nine kilograms. He was given 0.33 gm. three times a day. This dosage was continued for one day during which time the temperature ranged from 38° to 40° C., as it had for the four previous days. At the end of the first day the temperature dropped to normal and remained there. The sulfanilamide concentration at that time was 4.5 mg. per cent. Two days later a thoracotomy was done. The baby did extremely well. On May 28, 1937, just before the thoracotomy, the dosage of sulphanilamide was increased, one gram of sulfanilamide in 100 c.c. of normal saline solution being given subcutaneously and 1.3

gm. orally. The blood concentration before the increase was 1.9 mg. per cent. The following day at 11:00 A.M. it was 1.8 mg. per cent, and on May 31, 1937, it was 2.5 mg. per cent. The dosage of 0.1 gm. per kilogram failed to raise the blood sulfanilamide concentration to what is thought an effective level. After the first day of sulfanilamide therapy, the temperature dropped to normal and remained there. Whether or not this was a coincidence cannot be decided.

CASE 2.—R. B., a one-year-old white boy, was admitted to the hospital March 20, 1937, with a history of empyema following a lobar pneumonia of ten days' duration.

Physical examination revealed an acutely ill child who was dyspneic. There were definite signs of fluid on the left side of the chest with a shift of the heart to the right. This was confirmed by fluoroscopic examination. Both tympanic membranes were red and injected. Blood and chest fluid cultures subsequently grew a hemolytic streptococcus. His temperature course was septic in nature, ranging from 38° to 40° C. The chest was again tapped on March 23 and March 24, and considerable fluid removed which later grew a hemolytic streptococcus. On March 27, 1937, a closed drainage was instituted. Adequate fluid intake was maintained by parenteral administration of lactate-Ringer's and dextrose subcutaneously and intravenously. On the third and fourth day of admittance he was given 15 c.c. of prontosil intramuscularly, and started on 0.16 gm. sulphanilamide orally. During the following three days, his temperature gradually subsided. On the sixth day after admission the temperature again became septic. From this time on until he expired he was given 20 c.c. of prontosil intramuscularly daily. His course was progressively downhill. Autopsy: Bronchopneumonia, bilateral empyema, anterior mediastinitis. During his entire illness he looked so moribund that it is doubtful if larger doses of prontosil would have been helpful, although at this time we were not determining blood sulphanilamide concentrations, and knew little about the use of the drug.

CASE 3.—F. S., a two-year-old white boy, entered the hospital on Dec. 19, 1936, with empyema following lobar pneumonia in his left lung. He looked acutely ill. Blood and chest fluid culture revealed pneumococcus Type I. He was given 80,000 units of antipneumococcus serum. About one week after an open drainage, 15 c.c. of prontosil intramuscularly were started and continued for eight days until he expired.

CASE 4.—K. A. entered the hospital on April 13, 1937, with lobar pneumonia and empyema, pneumococcus Type I. Temperature course ranged from 39° to 40.5° C. She was given prontylin 0.16 gm. every four hours at the time a thoracotomy was done. The temperature three days later returned to normal and remained so until discharge.

It is quite obvious that the number of cases of pneumonia and empyema treated with sulfanilamide is too small to permit us to draw any conclusions about the value of sulfanilamide in such conditions.

V. PERITONITIS

CASE 1.—S. O., a ten-day-old white baby girl, was admitted to the hospital on April 2, 1937, because of restlessness and irritability. There were five to six loose stools on the day of admittance.

Physical examination revealed an acutely ill child who was dehydrated, malnourished, and had bilateral otitis media. The abdomen was distended, and there was an infection of the umbilicus. The liver was palpable two fingerbreadths below the costal margin. The temperature was 40° C. An abdominal paracentesis revealed pus, and many cocci were seen on smear. Hemolytic streptococcus was grown from the abdominal fluid and blood culture. About twelve hours following admittance

the patient was given 2 c.c. of prontosil and streptococcus antitoxin intramuscularly. She was also given parenteral fluids. She expired the day following admittance. This case was one of an overwhelming infection.

CASE 2.—B. R. This child was a case of chronic glomerulonephritis (nephrotic stage) who had been under our observation for one year. She had a good deal of edema. On Jan. 18, 1937, her temperature suddenly rose from normal to 39.6°. Her abdomen, which usually contained considerable fluid, was tense and distended, but not rigid. An abdominal paracentesis done on Jan. 19, 1937, revealed cloudy fluid containing very many polymorphonuclear leucocytes but was sterile on culture. Blood culture was negative. A few small erysipeloid areas were noted on her abdomen. She was given 15 c.c. of prontosil intramuscularly on Jan. 18, 1937; 20 c.c. on January 20, and 10 c.c. on Jan. 21, 1937. Sulphanilamide, 0.33 gm., was started Jan. 21, 1937, subcutaneously and orally. After her temperature remained elevated for two days it gradually came down to normal as the infection subsided.

VI. PYELITIS

CASE 1.—A. G. The first urinary tract infection in this child occurred in July, 1933, when she was fourteen months of age. The febrile period during this attack lasted ten days; the organism that was cultured was *B. coli*. An intravenous pyelogram indicated an anatomically normal genitourinary tract. She apparently had no further acute attacks, but when seen again in 1937 her urine was found to be hazy and contained pus. A catheterized specimen showed numerous colonies of *B. coli* on culture. No improvement followed mandelic acid therapy. Forty-eight hours after sulfanilamide therapy was started (0.7 gm. four times daily orally, plus 15 c.c. of molar sodium lactate four times daily), the urine became free of pus and was still sterile two days later.

CASE 2.—C. C., a six-year-old white girl, entered the hospital June 15, 1937, with the complaint of fever, chills, nausea, headache, abdominal pain, and frequency of a few hours' duration. There was a history of a mild upper respiratory tract infection two weeks before admittance, that had subsided. The abdominal pain was more severe on the right. Physical examination revealed a well-developed, well-nourished white girl, who was quite toxic, drowsy, and apathetic. There was some voluntary muscle spasm and tenderness in the right flank. The temperature was 40.5° C. on admission and she was given 30 c.c. per kilogram body weight of a one-sixth molar sodium lactate solution in order to relieve dehydration, promote diuresis, and alkalinize the urine. Her temperature rose for a short time to 42.3° C., and she looked very ill. The temperature then came down steadily by lysis. Her sulfanilamide therapy consisted of one gram in 100 c.c. of saline parenterally three times a day, and 0.5 gm. orally twice during the night. This was continued for two and one-half days, after which 2 gm. were given subcutaneously, plus the usual night dose. This was given for one day, and then all sulfanilamide therapy was discontinued because of the marked degree of cyanosis, which was undoubtedly due to the sulfanilamide therapy, and because the urine had become free of pus and was sterile. From here on her clinical course was uneventful.

VII. ERYSIPELAS

Some of our most satisfactory results with sulfanilamide therapy were obtained in cases of erysipelas (Table VIII). In all the cases there was an immediate cessation of the infection. A peculiar orange color was noted around the edge of the infected area in every case treated with prontosil. There was also a livid color in the patients who developed methemoglobinemia.

TABLE VII

DATE WT. 27 KG.	URINE				BLOOD						SULFANILAMIDE		
	ALBUMIN	MICRO UNCENTRIFUGED	CULTURE CATHETERIZED SPECIMEN	REACTION TO LITMUS	CO_2 VOL. PER CENT	DEXTROSE MG. PER CENT	LACTIC ACID	O_2 CAP. VOL. PER CENT	HB. BY O_2 CAP. GM. PER CENT	HB. BY SAHLI GM. PER CENT	PARENTERALLY	ORALLY	CONCENTRATION IN BLOOD, MG. PER CENT
6/15/37*			Paracolon	Alkaline							1.0 gm.	1.0 gm.	
6/16/37	+	15 W.B.C. H.P.F.	Paracolon	Alkaline	59.6	95.0					3.0 gm.	1.0 gm.	
6/17/37	+	5 W.B.C. H.P.F.	Few *B. coli*	Alkaline			14.0	14.5	10.8	11.6	3.0 gm.	1.0 gm.	5.8
6/18/37			Negative	Alkaline	48.0	98.0	17.9	13.0		11.6	2.0 gm.	1.0 gm.	11.4
6/19/37	++	8 W.B.C. H.P.F.	Negative	Acid	Methenamine 7.5 gr. every 6 hr.								
6/21/37			Negative	Acid	Methenamine 7.5 gr. every 6 hr.								

*30 c.c. ⅙ molar sodium or lactate per kg. I.V.

CASE 1.—J. L. Prontosil was started two days after admittance. Previous to its use, the temperature was continually high, averaging 40° C. Antierysipelas serum, citrated whole blood and ultraviolet ray had already been used. A sharp fall in the temperature followed the use of prontosil, and after 20 c.c. had been given intramuscularly, the temperature remained about normal for twenty-four hours. The erysipelas, however, had continued to spread downward, and had reached the foot, and we were of the impression that recovery was imminent, regardless of treatment, and, therefore, prontosil was discontinued. A remittent temperature recurred, however, and then serum sickness developed. On Jan. 6, 1937, the foot was extremely swollen, with the area of greatest redness on the dorsum; the leg also was swollen. It appeared to us that a cellulitis was developing, and we decided to give more prontosil. Rapid improvement of the appearance of the leg and foot followed, with a drop in the temperature and localization of the infection with the development of a sterile abscess.

CASE 2.—J. M. The infection was moderately severe but in less than twelve hours after institution of therapy, the temperature, which was 39.8° C. on admission, dropped to normal with a complete cessation of the spread of the infection. This patient returned Feb. 15, 1937, with an abscess of the area previously infected. This was incised and drained. Hemolytic streptococcus grew on culture. The child was not given any sulfanilamide by mouth during this hospital stay, nor during the period of convalescence at home.

CASE 3.—T. G. The erysipelas of the cheek as well as the abscess seemed to respond to the therapy. There was an upper respiratory tract infection that grew hemolytic streptococcus on culture. This was probably the cause for the temperature elevation, as the infected cheek improved with sulphanilamide. Three days after admittance when the upper respiratory tract infection subsided, the temperature fell to normal and remained there. Hot packs were also used.

CASE 4.—E. W. The patient had erysipelas of the neck that subsided in one day after sulphanilamide treatment was instituted. The infection was moderately severe. Magnesium sulphate packs were used.

CASE 5.—J. S. The child had a severe infection of the left leg. Upon admittance it was extremely red and angry looking. The following day treatment with prontosil intramuscularly was instituted and the infection ceased to spread. Sulphanilamide therapy was not continued after discharge from the hospital. Boric packs were applied to the infection.

CASE 6.—R. S., a one-month-old infant, had as severe a case of erysipelas as had been seen in the hospital for some time. About twelve hours after the sulphanilamide therapy was started the temperature dropped to around normal and remained there. This temperature drop was prior to the intravenous injection of citrated blood. Magnesium sulphate packs were applied constantly to the infection.

CASE 7.—G. L., a seven-month-old white boy, entered the hospital on April 2, 1937, because of bilateral chronic otitis media of one month's duration. A bilateral antrotomy was done on April 5, 1937, and hemolytic streptococci were grown on culture. Nine days after admission and six days after antrotomy, he developed erysipelas of the left cheek and ear, that subsided overnight: i.e., within twelve hours after the sulphanilamide was given.

CASE 8.—J. M. entered the hospital on May 15, 1937, with a full-blown erysipelas of the buttocks and lower abdomen. He was given sulfanilamide in a single dose the equivalent of 0.1 gm. per kilogram of body weight. He was then given the same amount in divided doses over twenty-four hours. His temperature on admission was 41.0° C. The following day he was given 50 c.c. of blood intravenously. Eight

TABLE VIII

DATE	AGE YR.	DURATION OF SYMPTOM BEFORE TREATMENT	LOCATION OF LESION	SPREAD AFTER THERAPY	INTERVAL BEFORE NORMAL TEMP.	ADMITTANCE TEMP. ° C.	WT. KG.	SULFANILAMIDE	BLOOD CULTURE	REMARKS
12/12/36 Case 1 J. L.	5/12	2 da.	Right thigh	None	36 hr.	40.5	7.9		Neg.	5 c.c. erysipelas serum, ultraviolet and blood I.V. Abscess developed.
2/3/37 Case 2. J. M.	1	1 da.	Face, scalp, and right ear	None	12 hr.	39.8	8.9	2/ 3 prontosil 5 c.c. I.M. 2/ 4 prontosil 20 c.c. I.M. 2/ 5 prontosil 10 c.c. I.M.	Neg.	Returned 2/15/37 with abscess.
1/29/37 Case 3 T. G.	19/12	4 da.	Left cheek	None	3 da.	40.0	12.5	1/29 prontosil 10 c.c. I.M. 1/30 prontosil 30 c.c. I.M. 1/31 prontosil 10 c.c. I.M.	Neg.	Nose and throat culture hemo. strep. Abscess drained 2/5/37.
3/13/37 Case 4 E. W.	5	1 da.	Left side of face	None	1½ da.	38.5	–	3/13 prontosil 10 c.c. I.M. 3/14 prontosil 10 c.c. I.M. Sulfanilamide 0.16 gm. every 4 hr. 3/13 to 3/20/37	Neg.	Nose and throat hemo. strep. $MgSO_4$ packs.
3/18/37 Case 5 J. S.	4	2 da.	From midthigh to knee	None	3 da.	40.0	–	3/19 prontosil 20 c.c. I.M. 3/20 prontosil 20 c.c. I.M. 3/21 prontosil 10 c.c. I.M.	Neg.	Temp. fell by lysis. Abscess drained 3/29—no growth.
3/24/37 Case 6 R. S.	1/12	2 da.	Diaper region, vulva, thighs	None	12 hr.	40.2	4.0	3/24 prontosil 5 c.c. I.M. 3/25 prontosil 7.5 c.c. I.M. 3/26 prontosil 7.5 c.c. I.M. 3/27 prontosil 2.5 c.c. I.M.	Neg.	Sulfanilamide 0.16 gm. every 6 hr. for 3 days. I.V. blood. $MgSO_4$ packs.
4/2/37 Case 7 G. L.	7/12	1 da.	Mastoid region	None	3 da.	40.3	8.0	4/12 prontosil 5 c.c. I.M. 4/13 prontosil 15 c.c. I.M. 4/14 prontosil 10 c.c. I.M.	Neg.	Sulfanilamide 0.33 gm. 4 times a day 4/16 to 4/20. Ear culture hemo. strep.
5/15/37 Case 8 J. M.	1/12	1 da.	Diaper region	None	24 hr.	41.0	3.5	Sulfanilamide 0.16 gm. every 4 hr. for 3 days	Neg.	Sulfanilamide 0.1 gm. per kilo as initial dose. $MgSO_4$ packs.
6/17/37 Case 9 D. M.	2½	4 da.	Right ankle to midthigh	None	24 hr.	39.5	13.0	Sulfanilamide 6/17 5 gm. 6/18 2.5 gm. 6/19 2.5 gm. 6/20 2.5 gm. 6/21 2.5 gm. 6/22 2.5 gm.	Neg.	All the sulfanilamide was given by mouth.

I.M. = Intramuscularly.

hours after sulfanilamide was started, his temperature dropped to 39° C., and then continued to fall until it was entirely normal the third day.

Cold magnesium sulphate packs were used daily for two days. The child developed a blue color and there was about 50 per cent methemoglobinemia by spectroscopic examination. There was also some sulphemoglobinemia.

CASE 9.—D. M. had a severe angry looking erysipelas infection of the right extremity, extending from the mid-thigh to the ankle. The temperature on admittance was 39.5° C., and ten hours after the sulfanilamide therapy was instituted the temperature began to fall. It was normal thirty-six hours after admittance. She weighed 13 kilograms, and was given 2.5 gm. as an initial dose, and then the same amount in divided doses over twenty-four hours.

It is interesting to speculate on the mechanism of the abscess formation noted with the use of sulfanilamide in erysipelas. Apparently the immunity developing in erysipelas is largely a cellular one, and of such a high degree that it is very rare to see abscess occur in a site recently affected. It is possible that the effect of sulfanilamide is to abort the infection and make unnecessary the development of such high degrees of tissue immunity, so that, if the drug is prematurely discontinued and organisms are still present, the infection terminates by abscess formation.

VIII. CELLULITIS AND ERYSIPELOID

CASE 1.—A. C. This child, with anasarca as part of nephrosis, apparently had been quite free of infection for at least two weeks previous to March 29, 1937. A sudden rise in temperature to 40° C. occurred on that date, associated with pain in the left lower abdomen. Soon a hyperesthetic and red area of the skin was noted in the left lower quadrant. This spread rapidly and soon involved the left thigh. Blood culture taken at the onset of this infection grew out *B. coli* and later when a small abscess was aspirated in the left thigh, *B. coli* was also grown from the pus. A pulmonary lesion also developed, accompanied by pain in the left chest, pleural effusion and continued fever. This infection gradually subsided, and the pleural effusion (the nature of which was never ascertained by thoracentesis) was reabsorbed. Altogether this infection lasted about three weeks. Treatment consisted of application of heat (infra red lamp) and daily transfusion of plasma.

A recurrence of redness of the skin over the lower abdomen with hyperesthesia and fever was noted on May 31, 1937. Sulfanilamide therapy was started on the day of the temperature rise, and within seventy-two hours the temperature was normal. It was discontinued three days after the temperature became normal. Three days later a recurrence of the skin infection was noted and sulfanilamide was resumed, and again in three days the temperature was normal. Sulfanilamide was continued after this infection for thirteen days, until June 19, 1937, and again on the third day following discontinuation of the drug, a recurrence of the skin infection was noted. This time the skin infection subsided and the temperature returned to normal five days after the therapy was started. The weight was 30 kilograms, about one-third of which was edema fluid. An initial dose of 3 gm. of sulfanilamide was given at the beginning of each infection (orally) and continued in a daily dose of 3 gm. divided into six doses.

The result of sulfanilamide therapy on the *B. coli* infection in this case becomes even more striking when one considers that shortly before and on several occasions during a period a few months previous to this infection, she had been given

I.M. = Intramuscularly.

large amounts of citrated whole blood or plasma, or human lyophile serum, in an effort to raise her plasma protein concentration.

CASE 2.—P. D., a five-year-old white girl, entered the hospital on March 19, 1937, with an abscess of the right ankle. A hemolytic streptococcus was grown from the pus. The ankle was red, and there was a diffuse swelling around the front of the internal malleolus. This area was fluctuant, and incision and drainage were instituted the day of admittance. Sulfanilamide, 0.33 gm., was given orally four times daily. Since the sulfanilamide and drainage were instituted at the same time, this case cannot be evaluated, although the second day after admittance the temperature was normal and remained normal until discharge.

CASE 3.—J. G. was a six-year-old white boy who had cellulitis of the scalp. Sulfanilamide therapy was instituted prophylactically just before discharge; i.e., after the area had healed.

CASE 4.—This patient was a ten-day-old male infant, who had a staphylococcus abscess of the lower lumbar region. He was given sulfanilamide subcutaneously and orally without any noticeable effects, and two days after the treatment was started, the area was incised and drained.

IX. OSTEOMYELITIS

CASE 1.—R. B. entered the hospital March 1, 1937, with a history of trauma of the right knee. He developed fever and was quite ill six days before his admittance. On admittance he appeared toxic. The temperature was 40.5° C. He had petechiae over his body, and there was tenderness of the right femur. Blood culture revealed *Staphylococcus aureus.* This same organism was grown from the right femur, which was drained. He developed other bone lesions and lung abscesses. There was also pericarditis. His temperature was of a septic nature. Prontosil, 20 c.c. twice daily, was given for the first four days, without change in the clinical course. His temperature remained elevated. Sulfanilamide, 0.66 gm., was given by mouth every four hours from the time of his admittance to the day he expired.

CASE 2.—W. W., a two-year-old white boy, was admitted to the hospital on March 15, 1937, with an acute osteomyelitis of the left femur. A culture taken from the operative site revealed *Staphylococcus aureus.*

He was again admitted to the hospital a short while after discharge with a soft tissue abscess at the same site as the previous operation. A culture of this pus grew both staphylococcus and hemolytic streptococcus. Sulfanilamide, 0.33 gm., was given four times a day after the temperature had started to subside. There was some clinical improvement, and the temperature remained normal. The streptococcus disappeared from the wound long before the staphylococcus.

X. SEPTICEMIA

CASE 1.—E. G. was a thirteen-year-old white girl who was admitted May 29, 1937, with a history of increasing pallor and unexplained fever of six weeks' duration. A positive blood culture *Staphylococcus aureus,* was obtained one week before admittance.

Physical examination revealed an anemic, malnourished child with an enlarged liver. There was a marked reduction in hemoglobin, red blood cells, white blood cells, and a relative lymphocytosis. Her condition became progressively worse, and all blood cultures taken until the time that she expired grew *Staphylococcus aureus.* Sulfanilamide therapy was instituted in doses of 0.2 gm. per kilogram body weight. Her temperature ranged between 40 and 41° C. and she soon developed classical signs of a staphylococcus pyemia. The sulfanilamide seemed to have little effect in this case.

CASE 2.—W. Y., an eleven-year-old white male, entered the hospital June 7, 1937, with a history of fever and discharging ear of two weeks' duration. The right ear ruptured spontaneously one week before admittance; no mastoid tenderness was noted. The child began to have intermittent temperature four days prior to admittance, accompanied by chills, headache, vomiting, and visual disturbance.

Physical examination revealed a well-developed, well-nourished boy, who was acutely ill. The fundi were normal. The neck was not stiff, nor were there any signs of meningeal irritation. The lumbar puncture on admittance yielded clear, sterile fluid. A Queckenstedt test was negative. A blood culture at this time subsequently grew a hemolytic streptococcus. Sulfanilamide therapy was instituted the second hospital day at which time he had a severe chill, the temperature rising from 37.5 to 41.5° C. Twelve hours after the sulfanilamide therapy was instituted, the temperature dropped to normal and remained so throughout the entire course. His weight was 24 kilograms, and he received sulfanilamide, 0.67 gm., every four hours for three days. An initial dose of 1.6 gm. was given orally at the onset of his treatment. It was felt that this patient benefited by the administration of this drug.

CASE 3.—R. R., a one-year-old white baby girl, entered the hospital June 17, 1937, with a history of eczema since birth that improved during the cool weather and recurred during warm spells. There was a definite family history of allergy. The baby did extremely well until six days prior to admission when she developed a cough and fever.

Physical examination revealed a child who was acutely ill. Her temperature was 41° C. and her respirations were rapid but not labored. The entire body was covered with an eczema which was secondarily infected. The chest was clear both as to physical examination and fluoroscopy. Blood culture at this time revealed a pneumococcus Type II. The leucocyte count was 17,450 with a marked shift to the left in the Schilling differential.

The child's weight was 9 kilograms, and sulfanilamide therapy was instituted the day of admittance. She was given an initial dose of 2 gm. subcutaneously, and 2 gm. were given orally on three successive days, plus one gram subcutaneously on the second day after admittance. After 2 gm. had been given orally on three successive days, the drug was discontinued, as the patient developed a deep cyanosis. The blood concentration at this time was 11.6 mg. per cent. Two days after the discontinuation of the drug the blood concentration was 1.4 mg. per cent. In addition to sulfanilamide, ten c.c. of sodium lactate were given orally three times a day, and parenteral lactate-Ringer's solution and blood were given on the fourth, fifth, and sixth days after admission. The day following the institution of sulfanilamide treatment the temperature dropped from 41° C. to 38° C., and three successive blood cultures were negative. On the third day after admittance the temperature rose to 40.7° C. and fell immediately by crisis. From this time on the convalescence was uneventful. All urines were alkaline to litmus. The serum CO_2 contents ranged from 38.3 to 42.6 volumes per cent.

XI. RHEUMATIC FEVER

CASE 1.—R. H., an eight-year-old white boy, a known active rheumatic with cardiac involvement and pericarditis, had been under treatment for some time. He had recently developed otitis media and had a reactivation of pericarditis at the same time. Hemolytic streptococcus was grown from the ear culture. He was given sulfanilamide, 0.33 gm., once a day for nine days, without any noticeable change in either his temperature curve or clinical course. The ear infection cleared up promptly.

CASE 2.—G. D., a fourteen-year-old boy, had chronic active glomerular nephritis with uremia, rheumatic fever, rheumatic heart disease, and maxillary sinusitis. About

three weeks after admittance prontosil was started because of symptoms and findings suggestive of peritonitis. This was discontinued when no organisms were cultured from the ascitic fluid. There was no noticeable improvement, and eventually the boy died of cardiac and renal failure.

XII. SCARLET FEVER

Sulfanilamide therapy was given to ten patients with scarlet fever. Six of these were moderately ill, none severely so. In most of these the dosage was very small. It is extremely difficult to evaluate the rôle that sulfanilamide played. In a few of these cases the clinical impression was that the streptococcus throat infection appeared to subside rapidly.

XIII. MISCELLANEOUS

Six children were given sulfanilamide, 0.33 gm., three times daily for three days prior to tonsillectomy and adenoidectomy. They were cases of malnutrition with chronic tonsillitis or rheumatism. No conclusions can be drawn, and the drug was given only for its prophylactic effect in preventing postoperative infection. In this it seemed successful. At the present time we are selecting various cases of cryptogenic infections, such as chronic infectious arthritis, as well as cases of typhoid fever and acute bacillary dysentery, to note any possible effect of sulfanilamide in these conditions.

COMMENT

Neither from our own experiences with sulfanilamide nor from those of others recorded in the literature do we feel that we really know the optimum concentration of the drug to be maintained in the blood, or the most desirable method of administering the drug. It is obvious, however, that in very sick infants and children, one should not rely on oral administration alone. Because such subjects are likely to need in addition to sulfanilamide therapy other supportive treatments, such as isotonic sodium lactate to relieve severe acidosis, lactate-Ringer's and dextrose solutions to relieve or prevent dehydration with less severe chemical changes, blood transfusions, etc., it seemed important to us to investigate the solubility of crystalline sulfanilamide in Ringer's solution, lactate-Ringer's solution, molar sodium *r*-lactate, and 10 per cent dextrose solutions. Solutions of one-fourth, one-half, three-fourths, and 1 per cent were made in each of the mentioned solutions, heated one-half hour in the boiling water-bath and allowed to cool. All the solutions remained perfectly clear, and no apparent change in pH was noted in the solutions of isotonic sodium lactate or lactate-Ringer's solution. It is our intention in the future to incorporate proper amounts of sulfanilamide in whatever solution is to be used for the patient in question.

An average blood sulfanilamide concentration of 10 to 15 mg. per cent seems usually to be effective for streptococcus, pneumococcus (exclusive of Type III ?), meningococcus, and colon bacillus (and related

organisms) infections. We are at present attempting to maintain such blood concentrations. It has been our experience that the daily dose of 0.1 gm. per kilogram body weight is very often insufficient for this purpose. Our present method of using the drug is to give an initial dose of 0.2 to 0.25 gm. per kilogram body weight, by the combined enteral and parenteral routes, and then to give a similar dose daily in divided amounts every four to six hours, day and night, if necessary to maintain the desired blood concentration of 10 mg. per cent. Such larger doses usually cause cyanosis and usually also cause hyperventilation which may be mistaken for dyspnea or acidosis. In subjects who otherwise had no good reason to develop acidosis, such hyperventilation quite uniformly was noted, together with slight reduction (10 to 15 volumes per cent) of the carbon dioxide contents of their bloods. Although we have not determined directly the pH of the bloods in these cases, the fact that the pH of the urine quite regularly is above 7, indicates that the blood change is really a carbon dioxide deficit type of alkalosis, in response to primary hyperventilation, and not one of mild acidosis. We have regularly failed to detect any significant increase in blood lactic acid during sulfanilamide therapy, despite deep cyanosis, hyperventilation, and serum carbon dioxide contents of 40± volumes per cent.

One, however, should be on the watch for the development of severe acidosis, since the conditions in which the drug is likely to be used are the very ones in which acidosis may sometimes occur: i.e., severe infections giving rise to serious lack of food intake, to circulatory failure, and renal insufficiency because of kidney damage or simply oliguria. If real acidosis does occur coincident with sulfanilamide therapy, we would expect it to be relieved quite promptly by therapeutic doses of isotonic sodium *r*-lactate, as happened in Case B. R., Table IX. It might well be worth while to administer prophylactically sodium lactate routinely with sulfanilamide to patients in danger of developing acidosis, just as it is the custom to administer alkali when large amounts of acetyl salicylic acid or sodium salicylate are prescribed. We had made this a routine before we realized that the usual blood change was that of alkalosis rather than acidosis. The alkali administration in these cases did not prevent the compensatory excretion of alkali into the urine and the maintenance of a subnormal serum bicarbonate level. Especially in urinary tract infections does sodium lactate administration seem indicated, since Helmholz has noted that excreted sulfanilamide is more bactericidal in alkaline than acid urine. Apparently 3 to 5 c.c. of molar sodium *r*-lactate per kilogram body weight (18 to 30 c.c. one-sixth molar) given daily in divided doses suffice to keep the urine properly alkaline in such infections, or to prevent acidosis.

The question of the advisability of administering the drug intrathecally has been raised. Our feeling at present is that, because the crystalline form of the material may be completely dissolved in Ringer's

TABLE IX

EFFECTS OF (1) DEXTROSE, (2) RINGER'S SOLUTION, AND (3) SODIUM LACTATE IN RELIEVING ACIDOSIS IN A CASE OF CHRONIC ACTIVE HEMORRHAGIC NEPHRITIS

PERIOD	DATE	TIME	CO_2 CONT. VOL. PER CENT	NaCl MG. PER CENT	N.P.N. MG. PER CENT	BLOOD SERUM					
						Na MM.	PROT. GM. PER CENT	ALB. GM. PER CENT	GLOB. GM. PER CENT	Ca MG. PER CENT	INORG. P MG. PER CENT
Before	2/25/37	7:45 P.M.	21.0	-	56.2	-	3.93	1.00	2.93	6.6	6.5
14 hr. after	2/26/37	10:00 A.M.	55.9	634	48.5						
150 c.c. molar Na r-lactate + 750 c.c. Ringer's solution + 150 c.c. 10 per cent dextrose I.V. and subcut.		Expected	(62.5)								
		Difference	-6.6								
Before	3/ 1/37	9:15 A.M.	23.3		70.9	133.4					
6½ hr. after	3/ 1/37	3:45 P.M.	26.2	644							
150 c.c. 20 per cent dextrose I.V. (40 c.c. isotonic/kg. b. wt.)		Expected	?								
Before	3/ 1/37	3:45 P.M.	26.2	644							
18 hr. after	3/ 2/37	9:40 A.M.	31.0	634	60.0	135.4					
780 c.c. Ringer's solution subcut. (38.7 c.c. isotonic or 6.67 M. Eq. B+/kg. b. wt.)		Expected	?								
Before	3/ 2/37	9:40 A.M.	31.0	634	60.0	135.4					
6 hr. after	3/ 2/37	3:30 P.M.	58.2	595		139.7					
780 c.c. ⅙ molar Na r-lactate I.V. and subcut. (38.7 c.c. "isotonic" or 6.67 M. Eq. B+/kg. b. wt.)		Expected	(64.5)								
		Difference	-6.3								

Case B. R. #M-830
Age = 3½ yr.
Wt. = 12.2 to 13.2 kg.
Duration of nephritis 2 yr.
Type: "nephrotic"
Urea clearance { 9/ 2/36 Cs = 67 per cent; 3/10/37 Cm = 42 per cent
Acidosis developed during period of acute infection associated with fever, vomiting, diarrhea, and oliguria, all of which had ceased before this period of study.
Urinary output (24 hr.)
2/23/37 = 1002 c.c.
2/24/37 = 770 c.c.
2/25/37 = 260 c.c. (onset of infection)
2/26/37 = 286 c.c.
2/27/37 = 571 c.c.
2/28/37 = 678 c.c. (no fever)
3/ 1/37 = 885 c.c.
3/ 2/37 = 1022 c.c.

Sulfanilamide therapy: prontosil, 45 c.c. I.M. between 1/18/37 and 1/21/37. Sulfanilamide 1.3 gm. daily from 1/21/37 to 3/5/37.

solution or "artificial spinal fluid" and seems not at all irritating, and because a high spinal fluid concentration should be desirable in cases of meningitis, we should continue its use by this route, at least until it has been more firmly established that oral or subcutaneous administration is equally as effective.

It has been demonstrated that the cyanosis which accompanies this form of therapy is due usually to methemoglobin and that sometimes sulphemoglobin also develops. Up to now,* methods for the determination of methemoglobin have been difficult or time-consuming or have necessitated the use of expensive apparatus. At Dr. Wendel's suggestion, we have followed our patients recently by determining simultaneously the oxygen capacity of fresh oxalated whole blood, and the total hemoglobin pigment by an acid-hematin method (Sahli or Newcomer). The difference represents methemoglobin plus sulphemoglobin, which in themselves are not dangerous, but become so only by replacing oxyhemoglobin. When oxygen capacities have dropped to a level the equivalent of 8 gm. per cent of hemoglobin (11.7 volumes per cent), we have considered it necessary either to discontinue the drug or reduce its dosage, or to transfuse the patient. Exsanguination transfusion should be kept in mind as an emergency measure should extreme symptoms develop as the result of excessive methemoglobin formation.

500 South Kingshighway
St. Louis, Missouri

*Dr. Wendel has just recently devised a very simple method for determining methemoglobin, which is apparently of sufficient accuracy to meet clinical needs. Under standardized conditions, oxalated blood is diluted to different degrees, and the highest dilution is noted in which the band characteristic of methemoglobin may be noted with a hand spectroscope. A previously constructed curve permits the worker to read directly volumes per cent methemoglobin.

REPORT ON SULFANILAMIDE FROM THE CHILDREN'S MEMORIAL HOSPITAL OF CHICAGO

JOSEPH BRENNEMANN, M.D.
CHICAGO, ILL.

IN OUR experience to date with sulfanilamide therapy we have noted an immediate favorable reaction in erysipelas and acute streptococcic ears and throats. In two cases of erysipelas the result was so prompt as to be positively shocking.

An interesting thing is the practically invariable effect on what might be called the hemolytic streptococcic carriers. In practically every case in which it has been tried the culture has been normal promptly, usually within twenty-four hours, but in every case the cultures have again become positive one to six days after sulfanilamide was stopped. In other words one gets from ordinary empirical clinical observation the idea that it does not destroy the organism but in some way or other prepares them for slaughter, or perhaps one might say stuns them for a while but does not kill them completely.

When one looks on the other side of this picture, there is some feeling of concern about the very profound changes that occur in the blood in nearly every case. One wonders whether there will not be cases of profound agranulocytosis such as are reported with pyramidon poisoning. The cyanosis is always a bit disturbing and is evidently not removed by putting the child in an oxygen tent. In our experience it has done no harm inasmuch as it recedes within a few days.

CASE REPORTS

CASE 79681.—Age ten years. Bilateral chronic suppurative otitis media following scarlet fever in 1934. Ear culture negative for hemolytic streptococcus; positive for proteus. Given sulfanilamide ten grains four times a day for four days. No improvement.

CASE 96308.—Age ten years. Acute bilateral otitis media for three days. Positive culture of hemolytic streptococcus in ears and nose and throat. High fever. Sulfanilamide: grain 10, q.i.d. for four days. Temperature dropped to normal twenty-four hours after treatment, ear stopped draining one week after treatment.

CASE 95989.—Age ten years. Bilateral suppurative otitis media for four years, chronic suppurative right hip one year. Negative nose and throat cultures for hemolytic streptococcus, also in ears, but positive *Bacillus pyocyaneus;* positive hemolytic streptococcus culture of hip. Given sulfanilamide, grain 10, t.i.d. for seven days. No effect upon ear; hip stopped draining for day or two and then drainage recurred after treatment stopped.

CASE 95367.—Age five years. Bilateral suppurative otitis media for one month. No temperature when treatment started. Ears positive for hemolytic streptococcus;

throat, occasional positive hemolytic streptococcus cultures. Given sulfanilamide 25 grains a day for seven days. Ears dry within twenty-four hours after treatment started.

CASE 85694.—Age two years. Acute suppurative otitis media bilateral. Nose, throat and ear cultures positive for hemolytic streptococcus. No temperature before treatment. Given 15 grains sulfanilamide daily for four days and 20 grains daily for three days. Marked improvement within forty-eight hours after treatment started with very slight drainage from one ear one week after treatment discontinued.

CASE 94389.—Age nine years. Chronic suppurative left otitis media following scarlet fever in January, 1933. Throat culture positive for hemolytic streptococcus. Ear culture negative for hemolytic streptococcus, positive for proteus. Given sulfanilamide, 40 grains, daily for five days. Ear stopped draining two days before treatment started and continued to be dry until six days after treatment was stopped when slight discharge occurred again.

CASE 96537.—Age, eighteen months. Fever, cervical adenitis, and bilateral otitis media for five days. Nose and throat cultures positive for hemolytic streptococcus and ear cultures positive for hemolytic streptococcus. Given sulfanilamide, 15 grains daily for two days. Temperature dropped to normal within twenty-four hours after treatment started. Stayed down for two days after treatment stopped after which it recurred again. Both ears stopped draining one day after treatment was stopped and stayed dry for four days after which the left ear started to have a slight mild discharge again. In this period the child had temperature and the left ear continued to drain for one week since which time it has been dry.

CASE 34765.—Age, nine years. Chronic bilateral otitis media, postmeasles in 1932; no fever. Given sulfanilamide, 5 grains t.i.d. for six days. No effect upon drainage of ear. Throat, nose, and ear cultures persistently negative for hemolytic streptococci but ear persistently positive for proteus bacilli.

CASE 48285.—Age, seven years. Bilateral otitis media, suppurative with left mastoid tenderness present twenty-four hours. Given sulfanilamide, 25 grains daily for six days. Temperature dropped to normal within twenty-four hours after treatment started. Left ear had practically no drainage two days after treatment started and practically dry one week after treatment stopped. Mastoid subsided during early treatment. Positive hemolytic streptococci from nose and throat.

CASE 49219.—Age, eleven years. Acute recurrent mastoiditis with pain in right ear for ten days. No drainage. Mastoid tenderness and swelling for four days. Nose and throat cultures negative. Right mastoid positive for hemolytic streptococcus. Right mastoidectomy two days before treatment started. Given sulfanilamide grains 10 q.i.d. for ten days. Temperature dropped to normal twenty-four hours after treatment started. Ear dry five days after treatment started. Wound completely healed the day treatment discontinued.

CASE 69438.—Age eight years. Right acute otitis media with mastoid tenderness. Cold for six weeks. Right earache, fever, cervical adenitis for four weeks, draining ear for three weeks, mastoid tenderness one week. Temperature before treatment. Culture from the ear: hemolytic streptococcus. From the throat: hemolytic streptococcus. Given sulfanilamide, 30 grains daily for seven days. Temperature dropped to normal within twenty-four hours after treatment was started and disappearance of mastoid tenderness. Ear dry twenty-four hours after treatment discontinued.

CASE 96678.—Age seven years. Cold two weeks; earache for one week with discharge and temperature; mastoid tenderness two days. Nose and throat cultures negative for hemolytic streptococcus. Left ear cultures positive for hemolytic streptococcus. Sulfanilamide given, grain 10 t.i.d. four days. Stopped for two

days and then grain 10 q.i.d. three days given. Temperature dropped to normal twenty-four hours after treatment started and mastoid tenderness disappeared only to recur when treatment stopped the first time and a mastoidectomy was done. Mastoid and ear continue to drain up to present time. There seemingly was a response to treatment at first but symptoms recurred and then no response to treatment.

CASE 53418.—Age twelve years. Cold for ten days with fever. Earache and mastoid tenderness for four days. Throat culture positive for hemolytic streptococcus. Ear culture positive for hemolytic streptococcus. Given sulfanilamide, 280 grains over a six-day period. Temperature dropped to normal twenty-four hours after treatment and ear stopped draining four days after treatment started.

CASE 69367.—Age seven years. Acute left suppurative otitis media and mastoid tenderness; pain in right ear with fever for two days. Swelling of right mastoid for one day. Temperature 104° F. Hemolytic streptococcus from nose and throat and from ear and mastoid. Given sulfanilamide, grains 30 for five days. Drop in temperature to normal and ear dry and mastoid wound healed four days after treatment was started.

Throat Infections

NURSE.—Age twenty-two years. Positive hemolytic streptococcus in throat for six months. Given sulfanilamide, 15 grains four times a day for three days. Culture less positive but remained positive after treatment.

NURSE.—Age twenty-six years. Positive hemolytic streptococcic throat for several days. Given sulfanilamide, grain 20 t.i.d. for three days. Culture became negative twenty-four hours after treatment started and remained negative for one week after which it became positive again.

NURSE.—Age twenty years. Positive hemolytic streptococcic throat for several days. Given sulfanilamide, grain 20 t.i.d. for one day and grain 10 q.i.d. for two days. Culture became negative forty-eight hours after treatment started and remained negative for one week after which it again became positive.

NURSE.—Age twenty-one years. Hemolytic streptococcus in throat cultures, positive for several days. Given sulfanilamide, 70 grains daily for two days after which culture became negative for four days and then became positive.

NURSE.—Age twenty-five years. Positive hemolytic streptococcic throat culture for several days. Given sulfanilamide, grain 15 five times a day for two days and grain 1 five times a day for one day. Throat culture became negative twenty-four hours after treatment stopped and remained negative for one week after which it became positive.

CASE 60548.—Age nine years. Stomatitis, tonsillitis. This had been present for one week with fever. Given sulfanilamide, grain 10 four times a day for two days. Temperature normal twenty-four hours after treatment started with rapid improvement although there was still some evidence of the stomatitis two weeks after treatment was discontinued. Nose and throat negative for hemolytic streptococci. Smear of gums: Many fusiform bacilli and spirillae.

Erysipelas

CASE 97595.—Age one year. Bronchial pneumonia, suppurative otitis media, streptococcus dermatitis simulating an erysipelas. High fever and cough for four days. Dermatitis of scalp for two days. Positive nose and throat cultures for hemolytic streptococcus; blood culture negative. Given sulfanilamide, grain 15 daily for three days. Temperature dropped to normal twenty-four hours after treatment

was started with a rapid subsidence of the streptococcic dermatitis within a few days. Practically no drainage from ears after opening. They became dry one week after paracentesis.

CASE 76303.—Age seven years. Erysipelas of left leg; abscess dorsum left foot. Pain and swelling in leg with high fever for two days. High temperature and chills for six days before treatment started. Hemolytic streptococcus culture positive from abscess of foot and from leg. Negative blood culture. Given prontosil, 2½ c.c. one day, 12½ c.c. next two days. Temperature dropped to normal twenty-four hours after treatment started and rapid subsidence of the erysipelas of the leg. Three days after treatment stopped, temperature rose, abscess of the dorsal of the foot developed which was evacuated. Discharge continued for three days. In this case the erysipelas was markedly benefited with seemingly no effect upon abscess formation.

CASE 96331.—Age twelve years. Erysipelas of the face of six days' duration with fever. Given sulfanilamide, grain 10 q.i.d. and prontosil 2½ c.c. q.i.d. for three days. Prontosil was then discontinued and the sulfanilamide given for three days more but was discontinued because patient developed a cyanosis which continued for four days. Temperature dropped to normal four days after treatment started. Clearing of the erysipelas began twenty-four hours after treatment started.

CASE 97550.—Age one year. Erysipelas of forehead secondary to laceration of the eyelid. Swelling and fever had been present for ten days before treatment started. Throat cultures positive for hemolytic streptococcus. Culture from erysipelas wound positive for hemolytic streptococcus. Sulfanilamide, 20 grains five times a day for five days with drop in temperature twenty-four hours after treatment started and subsidence of the erysipelas.

CASE 67112.—Age five years. Suppurative mastoiditis and erysipelas of the face. Earache, fever, swelling behind ear for seven days. Hemolytic streptococcus from mastoid. Nose and throat cultures, negative. Given 15 to 30 grains sulfanilamide daily for nine days. Erysipelas improved markedly four days after treatment started but the fever did not subside until after eight days of treatment. The mastoid gradually improved and there was only very slight discharge two weeks after treatment started. Marked improvement of erysipelas with questionable effect upon the mastoid.

Miscellaneous Conditions

CASE 65373.—Age seven years. Hemolytic streptococcic septicemia with pneumonia, jaundice, and a suppurative right hip. Abdominal pain and fever for two weeks and chills before admission to the hospital. Hemolytic streptococcus obtained from blood; nose and throat cultures negative. Hemolytic streptococcus from suppurative hip. Was given sulfanilamide, 15 grains t.i.d. for five days when she developed a slight cyanosis for two days. Treatment discontinued for ten days and then sulfanilamide, grain 15, t.i.d. for eight days was given. This child was a desperately ill youngster, and one is not sure but it seemed more than possible that the treatment has been of benefit to this child although she has not as yet completely recovered.

CASE 96924.—Age nine years. Hemolytic streptococcus peritonitis; hemolytic streptococcus from abdominal wound. Abdomen was opened and general peritonitis found. Put on prontosil 2½ c.c. q.i.d. for two days and then sulfanilamide 3½ gm. daily for two days after which treatment was discontinued for three days and sulfanilamide, grain 15 q.i.d. given for two days more. Temperature fell by lysis and child was making a slow recovery when there developed a pubic abscess at the present time. This again was a seriously ill child and it is hard to estimate the value of the treatment but we feel it has been of some benefit.

CASE P. P.—Age nine years. Had pneumonia five weeks before admission. Well for three weeks, then had daily and high septic fever with daily chill for ten days. Put on prontosil 5 c.c. t.i.d. for three days and then sulfanilamide 15 grain, t.i.d. for six days. The temperature dropped to normal and remained normal four days after treatment was started. Blood cultures negative on two occasions.

CASE P. P.—Age six months. Meningococcic meningitis; ill with fever for two weeks. On admission meningococci obtained from the spinal fluid. Was given forty thousand units of meningococci antitoxin on two successive days and again five days later. After the first dose of meningococci antitoxin, prontosil was given 5 c.c. one day, 2½ c.c. four times for the next four days; then sulfanilamide, grain 5 three times the following day. The temperature dropped to normal. The spinal fluid became negative six days after sulfanilamide treatment. The child was able to leave the hospital one week later well. Again it is impossible to attach much significance to the sulfanilamide in this case when three large doses of meningococcic antitoxin had been taken. Nose and throat cultures negative for hemolytic streptococci. Spinal fluid culture positive for meningococci for several days.

CASE 68586.—Age five years. Scarlet fever five months ago. Left mastoidectomy three months ago. Left otitis media for three months. Now for two days pain and swelling over left mastoid with fever for two days. Diagnosis: suppurative left otitis media and subperiosteal mastoid abscess. Mastoid and ear cultures negative for hemolytic streptococcus but positive for *Staphylococcus aureus*. Given sulfanilamide grain 15 q.i.d. for eight days. Mastoid abscess showed no drainage day treatment was stopped but ear continued to drain.

THE USE OF SULFANILAMIDE AS A URINARY ANTISEPTIC

SECTION ON PEDIATRICS, THE MAYO CLINIC

HENRY F. HELMHOLZ, M.D.,
ROCHESTER, MINN.

THE great interest aroused by the use of sulfanilamide in the treatment of various streptococcus infections has, for a time, diverted attention from its application as a urinary antiseptic. Early experiments[8] seemed to indicate that in the form of prontosil it had no effect in vitro on the colon bacillus, and inadequate dosage of prontylin resulted in negative therapeutic results.[1]

Temming[7] apparently was the first to use prontosil in the treatment of urinary infections. He gave the drug by rectal injection. The following year Unshelm,[8] Maraun,[5] Klein,[4] and Pernice[6] reported the successful use of prontosil in the urinary infections of childhood. Only Unshelm reported any in vitro experiments which were negative for bactericidal action on *Escherichia coli*. Klein gave prontosil intravenously in 8 per cent solution of dextrose because occasionally it caused vomiting and loss of appetite when given by mouth. Maraun reported failure on several occasions from insufficient dosage. Occasional vomiting and high coloring of urine and skin were the only complications. Unshelm reported good results in uncomplicated cases. His only untoward results were discoloration of skin and urine. His dosage of prontylin was as follows: for infants, 1½ to 2 tablets of 0.33 gm. each; for children from two to three years of age, 2 to 3 tablets; for children four to ten years of age, 3 to 4 tablets; and for children from ten to fifteen years of age, 5 to 6 tablets.

The marked coloring of the skin and urine makes treatment with prontosil definitely less desirable than treatment with prontylin, if the latter is equally efficient.

My interest in prontylin (sulfanilamide) as a urinary antiseptic resulted from in vitro experiments which showed it to have very marked bactericidal action on all of the common bacteria found in cases of infection of the urinary tract with the exception of the *Streptococcus faecalis*.[2, 3] The bactericidal action of the drug is manifest in both acid and alkaline urine, but apparently is more effective in a urine of alkaline reaction. The drug is present in the urine in both its free and conjugated forms, both of which seem to be bactericidal.

Experiments done with an acetylated form of sulfanilamide proved it to be less effective than the free form in the same concentrations and at the same pH. Concentrations of 50 mg. per cent of the free form, or of the free and conjugated forms, have bactericidal power in alkaline reaction.

The various urinary antiseptics must be considered in relation to their applicability to any patient in any stage of the disease. Methenamine in subacute and chronic infections of individuals whose urinary passages are normal is a very satisfactory drug but it is of little use for patients who have acute infections, urinary stasis, or reduced renal function. This also applies to the ketogenic diet and mandelic acid, each of which is dependent for its action on a certain degree of acidity of the urine. Furthermore, the necessity of controlling both the acidity and the concentration of the bactericidal substance in the latter two methods, makes successful use of them more difficult than is the use of sulfanilamide.

Taking drugs is not pleasant, particularly the carrying out of the ketogenic diet, and it results not infrequently in nausea and vomiting. Hematuria is a common result of treatment with methenamine. With both the ketogenic diet and mandelic acid, hematuria occasionally results. The three substances, methenamine, mandelic acid, and beta-oxybutyric acid, the potent factor when the ketogenic diet is used, are the most useful urinary antiseptics which have been available in the treatment of subacute and chronic infections. However they are not applicable to the acute stage of pyelitis, to any infection in which urinary alkalinity is maintained (infection with proteus) or to any case in which reduced renal function makes a urinary acidity of pH 5.5, and a certain minimal concentration of the drugs impossible.

Sulfanilamide fills in the above mentioned deficiencies. It can be given in the acute stage of the disease in addition to the usual forced intake of fluids and urinary alkalinization. In cases of infection with gram-negative bacilli, its action in the tissues has not been determined as yet. It has a more marked bactericidal action in an alkaline urine, so that it is ideal for use with alkalinizing treatment. It acts also in an acid urine, as is shown in a number of excellent therapeutic results in which the urine was constantly acid. However, in vitro experiments show that a higher concentration of the drug is necessary when the urine is acid in reaction. Administration of the drug usually produces an alkaline urine, thus producing satisfactory conditions for the action of the drug.

Its strong bactericidal action in alkaline urine is of especial advantage in the treatment of those infections associated with a strongly alkaline urine. Usually a urine of such reaction is brought about by infection with strains of *Proteus ammoniae* or with cocci, which split urea into ammonia. Seven strains of the *Proteus ammoniae* have been killed just as efficiently as have cultures of colon bacilli and of aerogenes, although one strain of *Proteus vulgaris* was slightly more resistant. This group of infections is the one which, because of the associated high pH, usually about 7.5 or 8.0, is resistant to treatment with mandelic acid.

A further advantage of sulfanilamide is its ease of administration as compared with mandelic acid or the ketogenic diet. The tablets are taken without difficulty after meals and at bedtime, and in our experience at the Mayo Clinic so far, they have not caused upset of the stomach. In the acute febrile stage of the disease they might do so, but in this stage prontosil could be given intravenously. A further advantage of sulfanilamide is its bactericidal activity when given to individuals whose renal function is reduced. In a case in which, for years, the urine had been milky with pus owing to infection with a colon bacillus, and in which the concentration of the blood urea constantly had remained between 75 and 100 mg. per cent since resection of posturethral valves three years before, we were able to render the urine clear.

Cook and Buchtel have reported two cases in which the concentration of blood urea was more than 100 mg. per cent but treatment was successful and the urine was rendered sterile.

German observers have reported only discoloration of the skin and urine and occasional nausea as complications. So far, with the dosage we have used, we have not seen complications. None of our children have had hemolytic anemia, dizziness, or headache, although we have been giving what I think we shall consider in the future fairly large doses for urinary infections. Our in vitro experiments and clinical results indicate that both the free and conjugated forms of sulfanilamide are bactericidal and that a concentration of 50 to 70 mg. per cent is bactericidal in an alkaline urine. We have given from 15 to 25 grains (1 to 1.6 gm.) in twenty-four hours and concentrations in the urine of between 100 and 200 mg. per cent have been reached. The concentration in the urine of an adult, after three days of a dosage of 30 grains (2 gm.) a day, reached 108 mg. per cent of the free form and 92 mg. per cent of the conjugated form in one specimen. Another patient, twelve years of age, who had renal insufficiency, after one week of a daily intake of 25 grains (1.6 gm.) had an output of only 26 mg. per cent of the free form and 24 mg. per cent of the conjugated form in the urine, with a concentration in the blood of 6.8 mg. of the free form and 2.0 mg. of the conjugated form. He was watched very carefully and after two weeks of medication he had no untoward symptoms except slight headache in the late afternoon.

A girl five years of age, and a boy three years of age, each received 25 grains (1.6 gm.) a day for four weeks and for two weeks, respectively. There were no ill effects from the treatment and the urine became sterile. The concentration of sulfanilamide in the urine in both instances was well above 100 mg. per cent.

Although much work needs to be done yet with dosage in relationship to urinary reaction, the following dosage is advised at present: For infants, 0.33 to 0.5 gm. per day; for children two to three years of age, 0.5 to 1.0 gm. per day; for children four to six years of age, 1.0 to 1.5

gm. per day; for those five to eleven years of age, 1.25 to 1.75 gm. per day; and for those twelve to fifteen years of age, 1.5 to 2.0 gm. per day. After four or five days of these dosages, the amounts can be reduced to three-fourths or two-thirds of the original dose. Cook and Buchtel gave the adult dosage at 30 grains (2 gm.) the first day, 40 grains (2.6 gm.) the second day, 60 grains (4 gm.) the third day, and 40 grains the days thereafter.

The effectiveness of the drug is seen in the three cases now to be reported. The first shows the effectiveness in an old chronic case; the other two, after failure with other methods of treatment.

CASE 1.—A girl, ten years of age, had had enuresis since the age of six years, with repeated attacks of urinary infection, manifested by urgency and burning. She had been under treatment a number of times but never had been adequately examined for evidence of cure. The general examination gave negative results except that evidence of a Ghon complex was found in the upper lobe of the right lung. The excretory urogram was negative. The concentration of blood urea was 34 mg. per cent. Urinalysis disclosed albumin grade 2 and pus grade 1. On culture, innumerable *Escherichia coli* grew in 0.5 c.c. of urine. We started treatment by giving 0.33 gm. of sulfanilamide five times a day. Forty-eight hours later the urine was sterile on culture. On the third day the pH of the urine was 6.0. The concentration of sulfanilamide in the urine was 78 mg. per cent of the free form and 112 mg. per cent of the conjugated form. On the third and fourth days, cultures of 0.5 c.c. of urine were sterile.

CASE 2.—A girl four years of age, was brought in suffering from chronic pyelitis with urinary stasis. She had been under observation and treatment for the past two years and had had one successful course of treatment with mandelic acid, with relapse. Six attempts over a period of two months, with mandelic acid and ketogenic diet, were made to try to rid the patient of the infection with *Escherichia coli*. We never were able to obtain two successive sterile cultures in a large number of positive ones. Sulfanilamide was then tried in doses of 0.33 gm. five times a day and after four days, the urine was sterile. Three days after use of the drug had been discontinued, there was a relapse. We repeated the same medication with sulfanilamide and after forty-eight hours the urine was again sterile. The urine continued to remain sterile after one week of giving 0.33 gm. five times a day and then one week of 0.33 gm. three times a day.

CASE 3.—The third case is that of a boy, three years of age, who had chronic urinary infection. The onset of the condition had been with a temperature of 105° F. Repeated trials with mandelic acid had been made at home in October, 1936 and in January, 1937. When the child came to us we had only temporary success with mandelic acid and after twenty-four hours the child had a relapse. We had no success with our further trials with mandelic acid or the ketogenic diet. We then tried sulfanilamide 0.33 gm. four times a day and after two days changed the dose to 0.33 gm. five times a day. On the fifth day the urine was sterile. We continued the same dose for one week and the urine remained sterile. Six days after the medication had been discontinued, the urine was still sterile.

The one great handicap of sulfanilamide as a urinary antiseptic is its total lack of bactericidal power for the *Streptococcus faecalis*. This organism grows luxuriantly in a urine that will rapidly kill the staphylo-

coccus and the various gram-negative bacilli. A patient, five years of age, was given 30 grains (2 gm.) of sulfanilamide a day, with urinary concentration of the drug reaching 98 mg. per cent of the free form and 68 mg. per cent of the conjugated form, in an attempt to clear up an infection with *Streptococcus faecalis*. At the end of five days the use of sulfanilamide was discontinued, as there still were innumerable organisms in 0.5 c.c. of urine on culture. Mandelic acid was administered and the infection cleared up in three days.

SUMMARY

Sulfanilamide on administration produces a urine that is strongly bactericidal for most of the organisms which cause infection of the urinary tract. The dosage which is necessary to produce bactericidal urine is considerably less than doses which have been given, without any ill effects, for infections with streptococci. Its ease of administration, its use in the acute stage of the disease, its action in an alkaline urine, and its successful use in cases of renal insufficiency, make it a drug of great usefulness in the treatment of acute and chronic infections of the urinary tract. It takes the place of other urinary antiseptics in its successful application to certain types of cases in which other substances have failed, but because of its lack of action on the *Streptococcus faecalis*, it cannot replace them entirely.

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STREPTOCOCCIC MENINGITIS

With Special Emphasis on Sulfanilamide Therapy

Walter H. Trachsler, M.D., George S. Frauenberger, M.D.,
Carl Wagner, M.D., and A. Graeme Mitchell, M.D.
Cincinnati, Ohio

GRAY[1] in 1935 in a comprehensive review of the literature on streptococcic meningitis listed for the period from 1901 to 1935 sixty-six cases in which recovery was recorded. The mortality rate, while difficult to evaluate, is obviously high. Schwentker and his coworkers[2] reported that none of 37 cases seen in the Johns Hopkins Hospital over a fifteen-year period recovered. Canfield[3] stated that of 33 cases treated at the University of Michigan Hospital recovery occurred in only one instance. Zeligs[4] reported that of 57 cases at the Cincinnati General Hospital in a fourteen-year period there was only one recovery. Tripoli[5] reported a mortality rate of 91.6 per cent from the State Charity Hospital of Louisiana for the 24 cases occurring between 1925 and 1934. Gray[1] estimates the mortality rate at 97 per cent. In his report he suggested that more interest be shown in such a fatal disease and that all cases be reported regardless of outcome in order that a more rational therapy could be evolved and more accurate figures secured for statistical purposes. Since that time an increasing number of cures has been reported.

We have attempted to review as completely as possible all the literature on this subject up to the present time (June, 1937). When recovery occurred the cases are listed in approximately the same manner as in Gray's paper. We have found 39 instances in which recovery occurred in addition to the 66 cases reviewed by Gray and now add 5 of our own, making a total of 110 recoveries.* In a few of the published cases it was impossible to decide whether a generalized streptococcic meningitis existed or only meningeal symptoms in a patient with streptococcic infection, these including the cases of Zischinsky,[6] Layton and coworkers,[7] and Shambaugh.[8] Only cases with reported positive findings in the spinal fluid, either in culture or on smear, are included in our figures. The occasional cases of mixed meningococcus and streptococcic meningitis are not mentioned. The number of unpublished recoveries is probably not great since such an outcome from this malady is uncommon enough to suggest reporting.

Various forms of treatment have been suggested for this highly fatal disease, their number indicating that all of them have been far from

From the Children's Hospital, Cincinnati, the Children's Hospital Research Foundation and the Department of Pediatrics, University of Cincinnati.

*The article by Neumann—Rev. Laryngol. Paris 55: 1, 1934, cited by Vitenson and Konstam[48]—was not available to us. This author is said to have reported three instances of recovery.

TABLE I

RECOVERIES IN STREPTOCOCCIC MENINGITIS NOT RECORDED BY GRAY[1]

AUTHOR	REFERENCE NUMBER	SEX	AGE	POSSIBLE SOURCE OF INFECTION	CULTURE OR SMEAR	TREATMENT
Hempstead	26	f	7	Otitis media; mastoiditis	Hemolytic streptococci	Complete mastoidectomy; spinal drainage.
Ebert	27	m	15	Rhinitis; sinusitis	*Streptococcus viridans* *Diplococcus catarrhalis*	Antimeningococcic serum intraspinally.
Tawse	28	f	11	Cold; otitis media	Hemolytic streptococci	Mastoidotomy.
Cann	29	f	19	Mastoiditis	Streptococci	Repeated lumbar punctures.
Crawford	17	f	2	?	Nonhemolytic streptococci	Repeated lumbar punctures; 5 c.c. of Pregl's solution intracarotid (3 days).
Idem (case of Dowman)	18	m	?	Mastoiditis	Streptococci	Continuous lumbar drainage; intracarotid injections Pregl's solution on 6 successive days.
Knichowiecki	31	?	4	-	Streptococci	Antistreptococcic serum.
Watson-Williams	32	f	49	Cold; otitis media	Streptococci	Mastoidectomy; lumbar punctures; antistreptococcic serum; collosol argentum, i.v.*
Kubie	9	?	13	Otitis media	Hemolytic streptococci	Forced spinal drainage.
Idem		?	15	Otitis media	Hemolytic streptococci	Forced spinal drainage.
Jory	7	m	7	Acute U.R.I.; otitis media	Hemolytic streptococci	Mastoidectomy; spinal taps.
Scott	35	m	6	-	Streptococci	Repeated lumbar punctures.
Gordon and Top	23	m	5	Scarlet fever; otitis media	Streptococci	Bilateral mastoidectomy; repeated lumbar punctures; scarlet fever streptococcic antitoxin, i.m.† and i.v.; polyvalent antistreptococcic serum, i.v.
Delger	24					
Zeligs	4	f	6	Skull fracture	Streptococci	Repeated lumbar punctures; antistreptococcic serum, i.v.; spontaneous drainage of spinal fluid from nose.

*Intravenously.
†Intramuscularly.

TABLE I—CONT'D

AUTHOR	REFERENCE NUMBER	SEX	AGE	POSSIBLE SOURCE OF INFECTION	CULTURE OR SMEAR	TREATMENT
Idem		m	11	?	Streptococci, green producing	Insufflation of air and repeated lumbar punctures.
Zischinsky	30	m	12	Scarlet fever	Hemolytic streptococci	Autogenous vaccine.
Greenfield	33	m	7	Otitis media; mastoiditis	Hemolytic streptococci	Mastoidectomy; subtemporal decompression; repeated spinal taps; transfusions.
Cracovaner	34	m	4½	Otitis media	Hemolytic streptococci	Mastoidectomy; spinal taps; antimeningococcus serum; transfusions.
Gangl and Zange	25	m	24	Otitis media	Hemolytic streptococci	Mastoidectomy; repeated drainage (suboccipital); urotropin.
Idem		f	8	Otitis media; mastoiditis	Streptococci	Mastoidectomy; repeated occipital punctures.
Marick	36	f	28	Hemorrhoidectomy in traumatized tissue	Nonhemolytic streptococci	Repeated spinal taps.
Poirier and Lovesey	37	m	4, 5	Acute U.R.I.; otitis media	Hemolytic streptococci	Repeated lumbar punctures; blood transfusion (no mastoidectomy).
Walker and King	14	f	28	Abortion	Hemolytic streptococci	Blood transfusions from individuals who had had scarlet fever.
Tripoli	5	f	12	Otitis media	*Streptococcus viridans*	Mastoidectomy; combined cisternal and lumbar punctures; polyval. antimeningococcus serum; intracarotid injection of 10% Pregl's solution.
Idem		m	16	?	Nonhemolytic streptococci	Combined cisternal and lumbar punctures; spinal fluid replaced by polyval. meningococcus serum.
Cadham	13	f	34	Otitis media	Hemolytic streptococci	Antistreptococcic rabbit serum, human serum.
Idem		f	32	Middle turbinectomy	Hemolytic streptococci	Polyval. antistreptococcic rabbit serum, human serum.
Williams and Simonton	38	f	13	Otitis media	Green producing streptococci	Complete mastoidectomy; continuous spinal drainage; transfusion.

TABLE I—CONT'D

AUTHOR	REFERENCE NUMBER	SEX	AGE	POSSIBLE SOURCE OF INFECTION	CULTURE OR SMEAR	TREATMENT
Lucas	39	m	9	Otitis media	Beta-hemolytic streptococci	Antimening. serum; antiscarlatinal serum, i.v.; prontosil solution and pront. album.
Schwentker, Clason, Morgan, Lindsay, and Long	2	f	6	Otitis media	Beta-hemolytic streptococci	Mastoidectomy; antimeningococcus serum intraspinally; transfusions; sulfanilamide.
Idem		m	13	U.R.I.	Beta-hemolytic streptococci	Antimening. and antistrep. serum; transfusions; sulfanilamide.
Idem		m	9	Otitis media, acute and chronic	Beta-hemolytic streptococci	Mastoidectomy; transfusions; sulfanilamide.
Vitenson and Konstam	40	m	10, 5	Otitis media	Beta-hemolytic streptococci	Mastoidectomy; repeated lumbar punctures; prontosil and prontosil album.
Frazer	41	m	17	Skull fracture	Hemolytic streptococci	Lumbar punctures; prontosil soluble and album.
Anderson	42	m	9	Otitis media	Hemolytic streptococci	Prontosil solution, i.m.; sulfanilamide.
Caussé, Loiseau, and Gisselbrecht	43	m	46	Otitis media	Hemolytic streptococci	Prontosil, i.v.
Weinberg, Mellon, and Shinn	22	m	17	Otitis media; mastoiditis	Hemolytic streptococci	Mastoidectomy; prontosil.
Idem		f	10	Cold; otitis media	Streptococci	Prontosil; sulfanilamide
Trachsler, Frauenberger, Wagner, and Mitchell		m	4½	Otitis media; mastoiditis	Hemolytic streptococci	Right mastoidectomy; antistreptococcic serum.
Idem		f	7	Otitis media; mastoiditis	Hemolytic streptococci	Mastoidectomy; antistreptococcic serum; blood transfusions; sulfanilamide.
Idem		f	9	Otitis media; mastoiditis	Hemolytic streptococci	Mastoidectomy; antistreptococcic serum; blood transfusions; sulfanilamide.
Idem		m	5	Otitis media; mastoiditis	Hemolytic streptococci Hemolytic staphylococci	Mastoidectomy; autogenous hemolytic staphylococcus vaccine; blood transfusions; sulfanilamide.
Idem		m	10	Otitis media; mastoiditis	Hemolytic streptococci	Mastoidectomy; antistreptococcic serum; sulfanilamide.

satisfactory. The procedure agreed on by all clinicians is the early surgical treatment of the primary focus of infection when this is possible, in order to prevent constant reinfection of the meninges.

In addition to the removal of the primary focus of infection, adequate drainage of the spinal fluid appears to be the most valuable procedure. It should be emphasized that at the first lumbar puncture only a few cubic centimeters of spinal fluid should be removed when it is clear, so that a localized meningitis may not be widely spread. Most of the recovered cases had some type of spinal drainage. In one case due to fracture of the skull (Zeligs)[4] recovery followed spontaneous drainage from the nose. Repeated lumbar punctures have been supplemented by cisternal punctures or surgical drainage of the cisterna magna. Continued drainage through a cannula without resort to operation has been employed.

Kubie[9] has reported some success following the use of "forced spinal drainage" by the administration of hypotonic solutions. Retan,[10] however, who prefers the term "forced perivascular drainage," feels that this method, in its present form at least, is not a cure for septic meningitis. The main danger in this procedure is that of a possible cerebellar herniation.

Spurling[11] does laminectomy, establishes continuous drainage, and forces the patient's intake of fluid so that 4 to 5 liters a day are ingested. This procedure leads to a tremendous output of cerebrospinal fluid. Gray[1] does not favor continuous drainage nor the removal of large amounts of spinal fluid at frequent intervals in cases in which the pressure is not excessive. He feels that it is putting too great a demand on structures that form the fluid and is liable to lead to their exhaustion.

The importance of air injections to break up intraspinal block and to facilitate drainage has been stressed.

Intermittent drainage of the spinal canal has been combined with the intrathecal injection of serum, either of a specific or a nonspecific nature. On the whole the results of the serum treatment in streptococcic meningitis have been discouraging.

Thalhimer and Levinson[12] treated seven cases of streptococcic meningitis with pooled convalescent scarlet fever serum. Though all seven patients died the authors believe "that early cases should not be denied treatment with large amounts of convalescent scarlet fever serum which might help in occasional cases."

Another type of serum treatment is reported by Cadham.[13] Two patients who recovered were treated with human serum and hyperimmune rabbit serum. Unfortunately the progress of the disease is often so rapid that there is insufficient time to stimulate the hyperimmunization of the rabbit with the organism isolated from the patient, a procedure which requires at least forty hours. The same difficulty holds for autogenous vaccines.

Blood transfusions have been used more widely in the last few years than formerly. Blood should be taken from donors with acquired immunity built up by working in hospitals (Gray)[1] or from persons who have recently recovered from scarlet fever (Walker and King).[14] There is apparently a better response when blood is given from donors who have had severe scarlet fever. Small transfusions should be frequently repeated.

Fleischmann[15] believes that disinfection of the meninges by way of the blood is possible and that the choroid plexus is permeable for drugs given intravenously. This, however, seems to be true only in cases of meningitis, since experimentally when the meninges are normal even fatal doses of drugs do not enter the cerebrospinal fluid. To obtain a higher concentration of the medicament in the meninges Kolmer[16] employed intracarotid injections which he states are simple and safe. Some encouraging results with injections of Pregl's iodine solution into the carotid have been observed by Crawford[17] and Dowman.[18] Gray[1] finds that this intracarotid injection is not necessary since sufficient concentration of the drug may be had by the usual venous route. Thrombosis of the cerebral vessels may follow this method of injection.

The unsatisfactory results of chemotherapy are well stated by Kolmer[19]: "So far as the administration of these chemical substances (ethylhydrocupreine hydrochloride, mercurochrome, metaphen, gentian violet, acridine dyes, acriflavine base, Rivanol and Pregl's iodine solution) by intravenous and intraspinal injections or by the two routes combined is concerned, I am satisfied that nothing is to be hoped for in the treatment of generalized or diffuse pneumococcus or streptococcic meningitis in either man or dog. With such results and experiences I abandon all hope of conquering septic meningitis by chemotherapeutic and biologic therapy until such time as more powerful antistreptococcic agents in vivo are discovered."

The last ten cases reviewed and four of our own cases have been treated with chemotherapeutic agents which are apparently more powerful than those just mentioned. The experimental work on the therapeutic use of sulfanilamide and its derivatives was started by Domagk,[20] who studied the effects of the original prontosil (hydrochloride of 4-sulfamido-2′:4′-diaminoazobenzene) on mice infected with hemolytic streptococci of human origin. Sulfanilamide (para-aminobenzenesulfonamide) rather than the original prontosil or other brands of it has been used more recently because of its greater solubility, convenience of administration, lesser toxicity, and the more favorable results obtained. The nature of the antibacterial action of these compounds is not yet completely understood but it seems to be a bacteriostatic one, possibly with the sulfanilamide as the active part of all of these drugs.

Within a few hours after oral and parenteral administration sulfanilamide appears in the blood stream and at a somewhat lower con-

centration in the spinal fluid. Because of this rapid absorption Colebrook and Kenny[21] came to the conclusion that there is no reason for injecting the drug intravenously. Parenteral administration may be used in the beginning of the treatment and if the patient is nauseated. Otherwise oral administration is a sufficient and a satisfactory method. Since the therapeutic activity of sulfanilamide appears to depend on its presence in adequate concentration in the blood, the rational method of treatment is the administration of relatively large initial doses followed by smaller ones sufficient to maintain a proper level of the drug in the blood over a considerable length of time. Schwentker and his coworkers[2] recommend as the best method of treatment in beta-hemolytic streptococcic meningitis a combination of oral and intraspinal therapy with sulfanilamide. They calculate the total dose for the first twenty-four hours on the basis of 1 gm. per 20 lb. of body weight up to a weight of 100 lb. The maximum dose for adults that may be used with safety should not exceed 5 gm. In fact such large doses may not be necessary since reports from England suggest that smaller ones are effective. For intrathecal use a solution in physiologic salt solution of 0.8 to 1.0 per cent is prepared. Fifteen to 25 c.c. of this solution at body temperature is permitted to flow into the spinal canal by gravity after a rather complete preliminary spinal drainage. Weinberg, Mellon, and Shinn,[22] however, state that the intrathecal administration should be employed only as a last resort since it is too hazardous a form of therapy. They have overcome the difficulty of the patient's inability to swallow the tablets by administering the drug by rectum.

The toxic effects of the drug are not yet well known and caution in administration is necessary. These effects may be transient nausea after oral administration, acidosis, cyanosis associated with sulfhemoglobinemia (or methemoglobinemia), pyrexia, jaundice, renal irritation, and also, in rare instances, acute hemolytic anemia and agranulocytosis.

CASE REPORTS FROM THE CHILDREN'S HOSPITAL, CINCINNATI

Since 1927 twenty-one children with proved cases of streptococcic meningitis have been admitted to the Children's Hospital of Cincinnati. Of the 14 patients received before Jan. 1, 1937, none of whom received sulfanilamide, only one recovered. During the first five months of 1937, seven such patients were admitted, four of whom recovered. All the 7 patients of this latter group received sulfanilamide or related compounds.

In the first group of 14 patients the meningitis was secondary to an acute purulent otitis media in all cases. Streptococcic septicemia was demonstrated in two of eight patients on whom blood cultures had been taken. In 13 of the 14 patients roentgenograms of the mastoid were taken, and in 12 of these cloudiness and cell destruction were demonstrated.

The definite diagnosis of streptococcic meningitis was made in each patient by positive spinal fluid cultures. Hemolytic streptococci were present in 11 cases, green-producing streptococci in two, and an intermediate streptococcus in one. Treatment before 1937 consisted of early eradication of the focus, the administration of antistreptococcic serum, and of blood transfusions. No chemotherapy was given.

In the one recovery listed in this group only a single positive culture of the spinal fluid was obtained. However, since a similar organism was found in the mastoid culture this case is included in our report, and the details are as follows:

CASE 1.—(Table II.) H. S., a white boy, four and one-half years of age, was taken ill two weeks before admission with an upper respiratory infection and a left purulent otitis media. He was admitted to the hospital on Dec. 15, 1936. He was acutely ill, his temperature being 105° F.; his pulse rate, 120; and his respiratory rate, 28. The left ear canal was discharging pus. A small perforation was found in the lower part of the drum. The mastoid was tender, but no swelling was present. The nose and pharynx were injected. The cervical lymph nodes were swollen, especially on the left side. Nuchal rigidity was present, although Kernig's and Brudzinski's signs were absent. The reflexes were normal. An unsustained, bilateral ankle clonus was elicited. A blowing systolic murmur was heard over the whole

TABLE II

CASE I

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
12/15/36	0	250	Neg.	None	None	None	None	None	Right mastoidectomy
12/16/36	1			None	None	None	None		
12/17/36	2			None	None	None	None		
12/18/36	3			None	None	None	None		
12/19/36	4	700	Neg.	None	None	None	None		
12/20/36	5	417	Hem. strep.	None	None	None	None		
12/21/36	6	1,015		Foshay serum*	10 c.c. i.m.†	None	None		
12/22/36	7	610	Neg.			None	None		Re-exposure of mastoid
12/23/36	8	208		Foshay serum	10 c.c. i.m.	None	None		
12/24/36	9			Foshay serum	10 c.c. i.m.	None	None		
12/25/36	10			Foshay serum	10 c.c. i.m.	None	None		
12/26/36	11			None	None	None	None		
12/27/36	12	21	Neg.	None	None	None	None		
1/ 1/37	17	10		None	None	None	None		
1/21/37	37	Discharged							

*Antistreptococcic serum prepared by Professor Lee Foshay, University of Cincinnati.

†Intramuscularly.

precordium. The examination was otherwise negative. The spinal fluid examinations are included in the summary (Table II). At first there was increased pressure, a ground-glass appearance, and increased globulin. The cell count always showed a preponderance of polymorphonuclear cells. The urine examination was negative. The white blood count was 26,750, with 95 per cent polymorphonuclear cells and 5 per cent lymphocytes.

Mastoid roentgenograms taken soon after admission showed cloudiness and destruction of cell walls on the left side. A slight haziness was also present on the right side. Four and one-half hours after admission a simple left mastoidectomy was performed. The mastoid cells were broken down and the cavity was filled with granulations and pus. The lateral sinus was normal. The culture of the pus showed hemolytic streptococci.

The temperature at first remained septic in type, but it fell to normal by the nineteenth day after admission and remained so thereafter. The spinal fluid culture on the fifth day contained hemolytic streptococci. On the seventh day the mastoidectomy wound was reopened and normal dura found. The treatment is given in the summary. Recovery was slow, but uneventful, except for a small abscess which developed on the left arm on the thirty-first day. The child was discharged from the hospital on the thirty-seventh day.

The final diagnosis was streptococcic meningitis, acute left mastoiditis, acute left suppurative otitis media, subsiding nasopharyngitis, and abscess of the left upper arm.

Four months later the patient was seen in the clinic. He had had two upper respiratory infections and had suffered from an attack of measles. Examination was negative and there were no complaints.

Subsequent case reports include those of all patients with streptococcic meningitis admitted to the hospital between January 1 and June 1, 1937. There were seven of these, all of whom received prontosil or prontylin or both. Treatment was usually started with the intravenous administration of prontosil soluble in 2.5 per cent solution, 5 c.c. being given every four hours for the first few days; then intramuscular injection was employed, and, as soon as the general condition improved, prontylin or sulfanilamide was given orally. In these cases there have not been severe reactions. Occasionally nausea and abdominal pain occurred with oral administration, and a rash which might be attributable to the drug.

In addition to chemotherapy all of these seven patients except two received antistreptococcic serum. One of these, who recovered, responded well to sulfanilamide therapy. He was also given an autogenous vaccine of hemolytic staphylococcus albus, since this organism was found in addition to the streptococcus in his spinal fluid. The other patient, who died, received no antistreptoccic serum because of a history of serum reaction and because of great sensitivity to horse serum when he was skin tested.

All cases due to otitis media had simple mastoidectomy performed. In the last three patients operation had been completed in less than six hours after admission. Mastoid roentgenograms were taken before

the operation. *If otitis media is found and mastoid tenderness is present, mastoidectomy should be performed in spite of a negative roentgenogram.*

Continuous intravenous injections of 5 per cent glucose in physiologic saline solution were usually employed. All but one patient received a series of small citrated blood transfusions.

CASE 2.—(Table III.) I. R., a white girl, seven years of age, was admitted to the hospital on Jan. 16, 1937.* For five weeks she had had a discharge from her left ear canal. The day prior to admission she developed persistent vomiting and com-

TABLE III

CASE 2

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
1/16/37	0	1,400	Hem. strep.	Commercial anti-strep.	20 c.c. i.m.†	Prontosil 2½%	5 c.c. i.v.‡ q. 4 hr.	100 c.c.	Mastoidectomy
1/17/37	1	1,300	Hem. strep.			Prontosil 2½%	5 c.c. i.v. q. 4 hr.	100 c.c.	
1/18/37	2	960		Foshay serum*	15 c.c. i.v.	Prontosil 2½%	5 c.c. i.v. q. 4 hr.	50 c.c.	
1/19/37	3			Foshay serum	30 c.c. i.m.	Prontosil 2½%	5 c.c. i.v. q. 4 hr.		
1/20/37	4			Foshay serum	30 c.c. i.m.	Prontosil 2½%	5 c.c. i.m. q. 4 hr.	100 c.c.	
1/21/37	5			Foshay serum	30 c.c. i.m.	Prontosil 2½%	5 c.c. i.m. q. 4 hr.		
1/22/37	6			Foshay serum	20 c.c. i.m.	Prontosil 2½%	5 c.c. i.m. t.i.d.	100 c.c.	
1/23/37	7			Foshay serum	10 c.c. i.m.	Prontosil 2½%	5 c.c. i.m. t.i.d.		
1/24/37	8	40	Neg.	Foshay serum	10 c.c. i.m.	Prontosil 2½%	5 c.c. i.m. b.i.d.		
1/25/37	9 10			None	None	Prontosil 2½%	5 c.c. i.m.		
1/26/37				None	None	Prontosil 2½%	5 c.c. i.m.		
1/27/37	11			None	None	Prontylin	5 gr. b.i.d.		

Discharged on Feb. 9, 1937. Between Jan. 28, 1937, and Feb. 9, 1937, 140 grains of prontylin had been given.

*Antistreptococcic serum prepared by Professor Lee Foshay, University of Cincinnati.

†Intramuscularly.

‡Intravenously.

*Patient of Dr. Benjamin Hoyer.

TABLE IV

CASE 3

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
2/1/37	0	775	Hem. strep.	Commercial anti-strep.	10 c.c. i. m.*	Prontosil 2½%	5 c.c. i. v. q. 4 hr.		
2/2/37	1			Commercial anti-strep.	10 c.c. i. m.	Prontosil 2½%	5 c.c. i. v. q. 4 hr.	150 c.c.	Mastoidectomy
2/3/37	2	795		Commercial anti-strep.	20 c.c. i. m.	Prontosil 2½%	5 c.c. i. v. q. 4 hr.	150 c.c.	
2/4/37	3	870	Hem. strep.	Commercial anti-strep.	20 c.c. i. m.	Prontosil 2½%	5 c.c. i. v. q. 4 hr.	75 c.c.	
2/5/37	4	Died 6:00 A.M.		None	None	Prontosil 2½%	5 c.c. i. m.	None	

*Intramuscularly.

plained of generalized headache and abdominal pain. Flexion of the neck became painful and delirium developed. When first seen she was critically ill, her temperature being 104.4° F.; the pulse rate, 116; and the respiratory rate, 32. A typical gun-hammer position was present. The left ear canal contained a foul-smelling purulent discharge. A small perforation was found in the lower left drum. There was mastoid tenderness. Marked stiffness of the neck and of the back muscles was present and Kernig's and Brudzinski's signs were positive. The spinal fluid showed increased pressure, slight cloudiness, normal sugar but an increased globulin content. There were 1,400 cells per c.mm., of which 80 per cent were of the polymorphonuclear variety. A direct smear showed a few gram-positive cocci in short chains. On culture hemolytic streptococci were found. The examination of the urine was negative.

The mastoid roentgenograms showed cloudiness on the left side, but the cell walls appeared to be intact. Twenty hours after admission a simple left mastoidectomy was performed. This disclosed extensive bone softening. The lateral sinus and the dura appeared normal. Prontosil was started immediately after operation. Commercial antistreptococcic serum was given intramuscularly just before operation. An antistreptococcic serum prepared by Professor Lee Foshay of the Department of Bacteriology was started on the third day. The therapy and the spinal fluid findings will be found in Table III.

The septic temperature fell by lysis and the temperature was normal on the eighth day. Convalescence was uneventful and the girl was discharged on the twenty-fourth hospital day.

The final diagnosis was streptococcic meningitis, acute left mastoiditis, and subacute, left, purulent otitis media.

CASE 3.—(Table IV.) W. B., a white boy, six years of age, developed a nasopharyngitis one week before admission. Two days later he complained of frontal headache, photophobia, and pain in his left ear. Three days before admission the left ear canal began to discharge spontaneously and there was relief from pain. However, nausea and vomiting developed. The day before admission the boy complained of pain in his neck and generalized hyperesthesia. Physical examination on admission (Feb. 1, 1937) disclosed an irritable, malnourished boy was who acutely ill, the temperature being 105.2° F.; the pulse rate, 148; and the respiratory rate, 40. Purulent, foul-smelling discharge was present in the left ear canal. A small perforation was found in the left tympanic membrane. Pressure over the left mastoid region caused pain. The posterior pharyngeal wall and the tonsils were injected. Nuchal rigidity and Brudzinski's and Kernig's signs were present. Superficial and deep reflexes were normal and equal. The spinal fluid was slightly cloudy, under greatly increased pressure, there were 775 cells per c.mm., mostly of the mononuclear variety. Direct smear showed gram-positive cocci in chains and the cultures subsequently demonstrated hemolytic streptococci. Urinalysis was negative. A blood culture taken on admission showed hemolytic streptococci.

In the mastoid roentgenograms there was cloudiness and also a lack of cell detail on the left. Five hours after admission prontosil and commercial antistreptococcic serum were started. A simple left mastoidectomy was performed sixteen hours after admission. Pus and bone destruction were found. In spite of the treatment the general condition remained poor and the boy died on the fourth hospital day.

The final diagnosis was streptococcic meningitis, streptococcic septicemia, left mastoiditis, left suppurative otitis media, and hypostatic pneumonia.

CASE 4.—(Table V.) S. R., a white girl, nine years of age, was admitted to the hospital on Feb. 21, 1937. For three months she had complained of intermittent attacks of pain in her left ear. No dischage was noticed. Two days before admission she developed high fever and delirium. In periods of lucidity she complained

TABLE V

CASE 4

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
2/21/37	0	720	Hem. strep.	Commercial antistrep.	10 c.c. i.m.	Prontosil 2½%	5 c.c. i.v. q. 4 hr.		
2/22/37	1	2,750	Hem. strep.	Foshay serum	10 c.c. i.m. 30 c.c. i.v.	Prontosil 2½%	5 c.c. i.v. q. 4 hr.		Mastoidectomy
2/23/37	2	1,975		Foshay serum	20 c.c. i.v. 10 c.c. i.m.	Prontosil 2½%	5 c.c. i.v. q. 4 hr.	100 c.c.	
2/24/37	3	975		Foshay serum	15 c.c. i.v. 15 c.c. i.m.	Prontosil 2½%	5 c.c. i.v. q. 8 hr.	100 c.c.	
2/25/37	4	1,580	Hem. strep.	Foshay serum	10 c.c. i.v. 10 c.c. i.m.	Prontosil 2½%	5 c.c. i.v. q. 8 hr.	100 c.c.	
2/26/37	5	900		Foshay serum	10 c.c. i.v.	Prontosil 2½%	5 c.c. i.m. q. 8 hr.	100 c.c.	
2/27/37	6	550	Hem. strep.	None	None	Prontosil 2½%	5 c.c. i.m. q. 8 hr.	100 c.c.	
2/28/37	7	1,440		None	None	Prontosil 2½%	5 c.c. i.m. q. 8 hr.		
3/ 1/37	8			None	None	Prontosil Prontylin	5 c.c. i.m. b.i.d. 5 gr. t.i.d.	100 c.c.	
3/ 2/37	9			None	None	Prontylin	5 gr. t.i.d.		
3/ 3/37	10	460	Neg.	None	None	Prontylin	5 gr. t.i.d.		
3/ 4/37	11			None	None	Prontylin	5 gr. t.i.d.		
3/ 5/37	12	310	Neg.	None	None	Prontylin	5 gr. t.i.d.		
3/ 6/37	13			None	None	Prontylin	5 gr. t.i.d.		
3/ 7/37	14	410	Neg.	None	None	Prontosil Prontylin	5 c.c. i.m. t.i.d. 5 gr. t.i.d.		
3/ 8/37	15			None	None	Prontosil Prontylin	5 c.c. i.m. t.i.d. 5 gr. t.i.d.		
3/ 9/37	16	447	Neg.	None	None	Prontosil Prontylin	5 c.c. i.m. t.i.d. 5 gr. t.i.d.		
3/10/37	17			None	None	Withheld	Withheld	100 c.c.	Re-exposure of mastoid
3/11/37	18			None	None	Prontosil Prontylin	5 c.c. i.m. t.i.d. 5 gr. t.i.d.		
3/12/37	19	245		None	None	Prontylin	5 gr. t.i.d.	100 c.c.	
3/13/37	20			None	None	None	None		
3/14/37	21	120		None	None	None	None	100 c.c.	
3/15/37	22			None	None	None	None		
3/16/37	23		Neg.	None	None	None	None		
3/17/37	24			None	None	Prontylin	5 gr. b.i.d.		
3/18/37	25	100		None	None				

Discharged on March 30, 1937. Between March 18 and March 30, 260 grains of prontylin had been given.

of occipital headache and photophobia. When first seen she was irritable and acutely ill. The rectal temperature was 105.5° F. The eyes appeared to be prominent and the left pupil was slightly smaller than the right. Both pupils reacted normally to light and accommodation. The right eardrum appeared normal but the left eardrum was thickened, grayish, and retracted. Mastoid tenderness and swelling were absent. The girl assumed a tripod position in sitting. Nuchal rigidity and Kernig's and Brudzinski's signs were present. Superficial and deep reflexes were hypoactive but equal. Unsustained ankle clonus was found on the left side. The spinal fluid was translucent with greatly increased pressure, contained 720 cells per c.mm., 60 per cent of which were of the polymorphonuclear variety. A direct smear was negative, but hemolytic streptococci grew rapidly in the culture. The urine was bloody, and contained a large amount of albumin. Examination of the sediment revealed many red blood cells, white blood cells, and granular casts. The white blood count was 23,600 with 91 per cent polymorphonuclear cells, 8 per cent lymphocytes, and 1 per cent monocytes. Two blood cultures remained negative.

Mastoid roentgenograms showed cloudiness and lack of cell detail on the left side. Left myringotomy released mucopurulent material which grew hemolytic streptococci on culture. Prontosil medication was started immediately after the organisms were found on smear in this pus. Shortly thereafter the patient received commercial antistreptococcic serum intramuscularly. The course of treatment is shown in Table V.

Twenty-six hours after admission the girl had a severe chill. A simple left mastoidectomy was performed twenty-nine hours after admission and a hemorrhagic mastoiditis revealed. Hemolytic streptococci were found in the culture of the pus. The septic temperature gradually fell by lysis. On the seventeenth hospital day the left mastoid region was reopened and necrotic bone removed. The dura and sinus were exposed and found to be normal. The urine became normal. The patient was discharged on the forty-sixth day.

The final diagnosis was streptococcic meningitis, left mastoiditis, left subacute otitis media and acute hemorrhagic nephritis.

On examination one month after discharge no abnormal symptoms or physical signs were present.

CASE 5.—(Table VI.) C. K., a white boy, twelve years of age, had a bilateral otitis media six weeks before admission. Both ears drained spontaneously two days after the onset with some relief of pain. Discharge was profuse for five weeks. During this time the boy had a low grade fever and frequent severe headaches. The week before admission he vomited, had fever, and complained of continuous, severe headache. The ear had ceased draining during this period but his general condition became much worse. Twenty-four hours before admission his neck and back became painful. He complained that he could not see clearly. The family history showed that one sibling had died of streptococcic meningitis. The boy was admitted on Mar. 12, 1937. He was semicomatose and assumed a gun-hammer position with an arched back and drawn up knees. His nutritional state was poor. His temperature was 99° F.; his pulse rate, 120; and his respiratory rate, 30. Both eardrums were gray. No pus was present. No mastoid tenderness or swelling was found. The eyes tended to move upward. The pupils were slightly dilated and reacted to light but not to accommodation. The neck was stiff and Kernig's and Brudzinski's signs were positive. Superficial and deep reflexes were normal. The spinal fluid was under increased pressure and cloudy, globulin was increased and sugar absent, there were about 5,000 cells to the c.mm., of which about 80 per cent were of the polymorphonuclear variety. A direct smear showed gram-positive organisms in chains, and on culture hemolytic streptococci were found. The urine was blood tinged and contained large amounts of albumin. In the sediment were numerous red blood cells and a few white blood cells, but no casts.

Discharged on March 30, 1937. Between March 18 and March 30, 260 grains of prontylin had been given.

TABLE VI

CASE 5

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
3/12/37	0	5,000	Hem. strep.	Foshay serum*	20 c.c. i.v.	Prontosil 2½%	10 c.c. i.v.	155 c.c.	Mastoidectomy, bilateral
3/13/37	1					Prontosil 2½%	20 c.c. i.m.†		Died 2:40 P.M.

*Antistreptococcic serum prepared by Professor Lee Foshay, University of Cincinnati.

†Intramuscularly.

TABLE VII

CASE 6

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
3/14/37	0	1,510	Green prod. strep.	None	None	None	None	None	None
3/15/37	1	2,100	Green prod. strep.	None	None	Prontosil 2½%	10 c.c. i.v.*	None	
3/16/37	2	2,600	Green prod. strep.	None	None	Prontosil 2½%	5 c.c. i.v.	None	
3/17/37	3	990		None	None	Prontosil 2½%	10 c.c. i.v.	None	
3/18/37	4	260		None	None	Prontosil 2½%	15 c.c. i.v.	None	
3/19/37	5	310		None	None	Prontosil 2½%	5 c.c. i.v.	None	
3/20/37	6	5,600	Green prod. strep.	None	None	Prontosil 2½%	10 c.c. i.v.	None	
3/21/37	7	Pus		None	None	Prontosil 2½%	20 c.c. i.m.† 5 c.c. i.v.	None	
3/22/37	8	Pus		None	None	Prontosil 2½%	10 c.c. i.m.	None	
3/23/37	9	Pus		None	None	None	None	None	
3/24/37	10	Pus		None	None	None	None	None	
3/25/37	11		Died	None	None	None	None	None	

*Intravenously.

†Intramuscularly.

Mastoid roentgenograms showed bilateral cloudiness with intact cell walls. Prontosil, antistreptococcic serum, and a transfusion were given shortly after admission. Bilateral myringotomy and simple mastoidectomy were performed. The right mastoid contained only a small amount of pus but a large amount was found in the left mastoid. After operation the temperature rose shortly to 107° F. and respirations ceased three hours after operation.

The final diagnosis was streptococcic meningitis, bilateral mastoiditis, and bilateral, subacute, purulent otitis media.

CASE 6.—(Table VII.) E. S., a white boy, twelve years of age, was admitted to the hospital on Mar. 14, 1937. Twenty-four hours previously he had been thrown against an automobile windshield. There were lacerations of the eyelids and profuse bleeding from the nose. Emergency treatment was given in a local hospital. No roentgenograms were taken. That evening he vomited several times. The morning of admission he had complained of severe headache and had vomited everything taken. He became drowsy and slept most of the day. Breathing became labored. On admission the boy was almost stuporous and his condition was critical. The rectal temperature was 105° F.; the pulse rate, 172; and the respiratory rate, 32. Lacerations were present about the swollen eyelids. The pupils were contracted and did not react to light or accommodation. A small perforation was found in the right eardrum. No blood or discharge was present. The mucous membrane of the nose was swollen and bloody discharge was found in both nostrils. The skull appeared normal on physical examination. Rhonchi were present over the bases of both lungs. Nuchal rigidity and Brudzinski's and Kernig's signs were present. The superficial and deep reflexes were normal. The spinal fluid was cloudy and under increased pressure, globulin was present, there were 1,510 cells per c.mm., of which 75 per cent were of the polymorphonuclear variety. A smear showed gram-positive cocci, and the culture green-producing streptococci. Skull roentgenograms revealed no evidence of fracture. Prontosil was started twenty-one hours after admission. Sodium luminal was given intravenously for restlessness. Daily spinal taps were performed. Serum was not administered because of a marked hypersensitivity to horse serum. The clinical condition became gradually worse and on the eighth hospital day the patient became comatose and remained so until death on the eleventh day.

The final diagnosis was basal skull fracture and streptococcic meningitis.

CASE 7.—(Table VIII.) V. M., a white boy, five years of age, had suffered from "flu" two weeks before admission. He had developed a draining left ear with persistent left frontal headache. Nuchal rigidity was noted. On Mar. 5, 1937, the boy was admitted to the Cincinnati Contagious Disease Hospital with a tentative diagnosis of meningococcus meningitis. Spinal tap revealed 600 cells per c.mm., mostly of the polymorphonuclear variety. No organisms were seen on direct smear. Thirty cubic centimeters of antimeningococcus serum was given intrathecally. Spinal fluid culture the following morning showed gram-positive cocci and the patient was transferred to the Children's Hospital.

Physical examination showed an acutely ill boy, his temperature being 104° F.; his pulse rate, 140; and his respiratory rate, 36. The left ear was discharging thin, purulent material from a perforated drum. The left mastoid region was tender upon pressure. Nuchal rigidity and Brudzinski's and Kernig's signs were present. The deep reflexes were slightly hyperactive. The spinal fluid was cloudy and contained 540 cells per c.mm., the majority of them of the mononuclear variety. Hemolytic streptococci were found in the culture. The blood examination showed 16,800 cells, 83 per cent of these being polymorphonuclears; 1 per cent, eosinophiles; 9 per cent, lymphocytes; 6 per cent, monocytes; and 1 per cent myelocytes.

The mastoid roentgenograms showed cloudiness on the left side. Prontosil was given intravenously shortly after admission. A simple left mastoidectomy was per-

TABLE VIII

CASE 7

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
3/ 6/37	0	600	Hem. strep.	None		Prontosil 2½%	5 c.c. i.v.q. 4 hr.		Left mastoidectomy
3/ 7/37	1	450	Hem. strep.	None		Prontosil 2½%	5 c.c. i.v.q. 4 hr.		
3/ 8/37	2	810	Neg.	None		Prontosil 2½%	5 c.c. i.v.q. 4 hr.	125 c.c.	
3/ 9/37	3	330	Hem. staph.	None		Prontosil 2½%	5 c.c. i.m. t.i.d.	115 c.c.	
3/10/37	4	160	Neg.	None		Prontosil 2½%	5 c.c. i.m. t.i.d.	125 c.c.	
3/11/37	5	80	Hem. staph. albus	None		Prontosil 2½%	5 c.c. i.m. t.i.d.	125 c.c.	
3/12/37	6	100		None		Prontosil 2½%	5 c.c. i.m. t.i.d.		
3/13/37	7	100	Neg.	None		Prontosil 2½%	5 c.c. i.m. t.i.d.		
3/14/37	8	95	Hem. staph. albus	None		Prontosil 2½%	5 c.c. i.m. t.i.d.		
3/15/37	9	100		None		Prontosil 2½%	5 c.c. i.m. t.i.d.		
3/16/37	10	100		None		Prontosil 2½%	5 c.c. i.m. t.i.d.		
3/17/37	11	100	Hem. staph. albus	None		None	None		
3/20/37	14	100	Neg.	None		None	None		
3/21/37	15		Hem. staph. albus	None		None	None		
3/23/37	17	100		None		None	None		
3/24/37	18		Hem. staph. albus	None		None	None		
3/25/37	19	710	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.		
3/26/37	20	800	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.		
3/27/37	21	810	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.	125 c.c.	
3/28/37	22	800	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.		
3/29/37	23	800	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.	125 c.c.	
3/30/37	24	4,000	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.		
3/31/37	25	950	Hem. staph. albus	None		Prontylin	5 gr. t.i.d.		
4/ 1/37	26	770	-	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/ 2/37	27	350	-	Autog. hem. staph. vac.		Prontylin	5 gr. t.i.d.		
4/ 3/37	28	200	-	Autog. hem. staph. vac.		Prontylin	5 gr. t.i.d.		

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		CITRATED BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
4/ 4/37	29	200	-	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/ 5/37	30	130	Neg.	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4 /6/37	31	40	Neg.	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/ 7/37	32	2	Neg.	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/12/37	37	2	-	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/21/37	46	2	Neg.	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/28/37	53	2	Neg.	Autog. hem. staph. vac. started		Prontylin	5 gr. t.i.d.		
4/29/37	54	Discharged							

formed two and one-half hours after admission. The bone was soft and the temporal plate very thin. Culture showed hemolytic streptococci. After each intravenous injection of prontosil the patient complained of severe abdominal pain. Spinal fluid culture on the third hospital day was reported to contain hemolytic staphylococcus albus, no streptococci being found at this time. The patient's condition, however, gradually improved. On the eighteenth day a culture of the pus from the ear showed hemolytic streptococci and hemolytic staphylococcus albus. A vaccine made from the staphylococcus was administered and the spinal fluid became sterile on the thirtieth day. The patient was discharged from the hospital on the fifty-fourth day after an uneventful recovery.

The final diagnosis was meningitis due to hemolytic streptococcus and to hemolytic staphylococcus albus, acute purulent left otitis media, acute left mastoiditis, and nasopharyngitis.

Two weeks after discharge the patient was reexamined. A slight residual bilateral ankle clonus was present and Babinski's sign was positive. Two weeks later the physical examination revealed no abnormality.

CASE 8.—(Table IX.) H. S., a white boy, ten years of age, had had measles six weeks before admission. Three weeks later the right ear began to discharge. Six days before admission the boy complained of double vision and later developed severe generalized headache and high fever, and became irrational. He was admitted on May 9, 1937. His temperature was 105.2° F.; his pulse rate, 160; and his respiratory rate, 26. At times he was delirious. A purulent discharge was found in the right ear canal. Pressure over the right mastoid tip caused pain. The eye movements were uncoordinated. The pupils were symmetrical but did not react to light or accommodation. The posterior pharyngeal wall was injected. There were a few moist râles at the bases of both lungs. Nuchal rigidity and Kernig's and Brudzinski's signs were present. The deep reflexes were hypoactive but equal. No ankle clonus was found. The spinal fluid showed increased pressure, was cloudy, and contained 5,000 cells to the c.mm., mostly of the polymorphonuclear variety.

Both smear and culture were negative. The white blood count was 23,400. Blood culture was negative and the urine examination revealed nothing abnormal.

Mastoid roentgenograms showed haziness of the right mastoid cells especially about the tympanic area, but cell structure appeared to be intact. The left mastoid was normal. Four hours after admission a right simple mastoidectomy was performed, but only a small amount of bone involvement was found. The middle fossa was exposed and the dura was found to be normal. Culture of the right mastoid contained hemolytic streptococci.

On the third hospital day culture of the spinal fluid showed hemolytic streptococci. On the fourth day strabismus became more marked and a right facial weakness developed. Treatment with prontylin was started. Later the patient received antistreptococcic serum intravenously. By the seventh day the temperature had fallen to 100° F. and the patient's general condition was much improved. There were three consecutive positive spinal fluid cultures. The culture on May 14, 1937, was negative and remained subsequently negative. The treatment is shown in Table IX. On the ninth day the temperature rose to 104.2° F., and two days later an urticaria developed and continued for several days. This eruption was considered to be a serum reaction, although the possibility that it might be a toxic effect of the sulfanilamide could not be definitely excluded. Prontylin was discontinued. Three days later the high fever which had accompanied the rash ceased, although a low grade fever continued for several days before the temperature finally became normal. There remained a paralysis of the right sixth cranial nerve but the patient's condition is otherwise excellent.

The final diagnosis was streptococcic meningitis, right mastoiditis, and right purulent otitis media.

TABLE IX

CASE 8

DATE	DAY	SPINAL FLUID		SERUM		SULFANILAMIDE		BLOOD TRANSFUSION	OPERATION
		CELLS	CULTURE	TYPE	ROUTE AND QUANTITY	TYPE	ROUTE AND QUANTITY		
5/ 9/37	0	5,000	Neg.	None	None	None		None	Mastoidectomy
5/10/37	1	2,800	Neg.	None	None	None		None	
5/11/37	2	600	Neg.	None	None	None		None	
5/12/37	3	2,100	Hem. strep.	None	None	Prontylin	40 gr.	None	
5/13/37	4	2,300	Hem. strep.	Foshay serum	20 c.c. i.v.	Prontylin Prontosil	45 gr. q.d. 20 c.c. i.v.	None	
5/14/37	5	1,500	Neg.	Foshay serum	40 c.c. i.v.	Prontylin Prontosil	90 gr. q.d. 30 c.c. i.v. q.d.	None	
5/15/37	6	900	Neg.	Foshay serum	40 c.c. i.v.	Prontylin Prontosil	90 gr. q.d. 15 c.c. i.v.	None	
5/16/37	7	1,345	Neg.	Foshay serum	20 c.c. i.v.	Prontylin Prontosil	90 gr. 15 c.c. i.v.	None	
5/17/37	8	1,100	Neg.	None	None	Prontylin Prontosil	90 gr. 10 c.c. i.m.	None	
5/18/37	9	900	Neg.	None	None	Prontylin	90 gr.	None	
5/19/37	10	880	Neg.	None	None	Prontylin	90 gr.	None	
5/20/37	11	400	Neg.	None	None	Prontylin	90 gr.	None	
5/21/37	12	150	Neg.	None	None	Prontylin	90 gr.	None	
5/22/37	13	110	Neg.	None	None	Prontylin	90 gr.	None	
5/23/37	14	70	None taken	None	None	Prontylin	45 gr.	None	
5/24/37	15					None	None		

COMMENT AND DISCUSSION

In addition to the 66 instances of recovery from streptococcic meningitis contained in the review by Gray in 1935, we have found reports of 39 other such cases and add five of our own, thus making a total of 110 recorded recoveries from streptococcic meningitis which appear to be acceptable.

Various forms of treatment have been employed for this highly fatal disease. These consist in early surgical treatment of the primary focus of infection and drainage of spinal fluid. In addition antistreptococcic sera and other sera such as convalescent scarlet fever serum have been employed. Blood transfusions have also been widely used. Most of the so-called chemical disinfectants have proved quite valueless with the exception of sulfanilamide and its derivatives.

All of the seven patients with streptococcic meningitis seen by us in the past five months were treated with sulfanilamide and its derivatives. In addition to the chemotherapy all seven of our patients except two received antistreptococcic serum and one of these, who received sulfanilamide therapy alone, recovered. Most of our patients were treated also by transfusion and by parenteral administration of fluids.

Four of the seven patients recovered. In addition we record the case of one patient who survived but who was not treated with sulfanilamide.

In none of our patients did any serious toxic manifestations occur from the drug.

We would like to stress the importance, in spite of an apparently negative roentgenogram, of early surgical treatment of the primary focus when this occurs in the mastoid.

We cannot help but be favorably impressed by the effect of sulfanilamide and its derivatives in the treatment of streptococcic meningitis. Of 71 patients whose case records were studied by us or who were seen either in the Children's Hospital or in the Cincinnati General Hospital before the use of this drug, only two recovered, whereas of seven patients treated with these drugs four recovered. Since our patients were also treated by other methods such as with antistreptococcic serum, transfusions, and parenteral injections of fluid, no suggestion can be made as to the possible effect of sulfanilamide alone.

After this paper was finished, M. B. Gordon, A. M. Litvak, and V. Caronna published a paper on streptococcic meningitis and abscess of the brain complicating scarlet fever (Am. J. Dis. Child. **53**: 1447, 1937). Two children with streptococcic meningitis recovered after the administration of antiscarlatinal serum. The authors also mention a recovery reported by J. C. Stratton (J. Am. Inst. Homeop. **27**: 70, 1934).

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Critical Review

SURGICAL PEDIATRICS

HERBERT E. COE, M.D.
SEATTLE, WASH.

THE practice of pediatrics is a definite and well-recognized specialty although many more children are cared for by general practitioners than by pediatricians. To a much greater degree surgical conditions in children are treated by the general practitioner and general surgeon than by the pediatric surgeon. Adequate surgical care for children does not demand that the surgeon restrict his practice to certain age limits. Such restriction is not possible or even desirable in most localities. It is, however, essential that he be possessed of more than average surgical ability and that he have a keen appreciation of the fact that the surgery of infants and children differs fundamentally from that of adults. The majority of the conditions in adults which demand the careful study and concentrated attention of the surgeon rarely or never occur in children and the converse is equally true. The fact that a child is small does not mean that the surgical problems involved are insignificant. The infant is not a diminutive adult and his surgery is by no means merely adult surgery scaled down.

The surgery of infancy and childhood has a peculiar fascination of its own.[1] At first there is the rapid adjustment to independent existence occasioned by sudden transition from an environment which is ideal for protection and the constant supply of nutrition to one which is characterized by an infinite number and variety of more or less violent sensory stimuli. Growth and development are rapid. At no other period does the weight of the individual double in six months; and from infancy to adolescence, changes of a profound character are rapidly taking place. One of the characteristics of the newborn is the ability to withstand the oftentimes severe trauma of birth, and this applies also to surgical procedures as seen in the repair of exomphalos, anastomosis for intestinal atresia, or even resection of the proximal half of the colon.

In early childhood prompt diagnosis and treatment of acute abdominal conditions is particularly necessary because of the extremely rapid progress of inflammatory lesions and the fact that during this period of growth dehydration and interruption of nutrition produce more profound and serious effects than later. Endocrine balance is easily disturbed as seen in the occurrence and serious consequences of acidosis. Diagnosis requires conscious and subconscious evaluation of many and diverse factors and the adjustment of methods to the individual peculiarities of the case. The adult comes to the surgeon voluntarily for relief, the child is often brought in spite of his active opposition. The parents' decision whether or not to submit a child to surgery is often influenced by family finances and by the marvelous physical adaptability and adjusting power of childhood which have brought him safely through previous supposedly similar conditions. Special care

of the infant and small child upon the operating table is necessary to prevent loss of body heat, and postoperative attention to fluid and food requirements is vital. The zone of safety in anesthesia is narrower than in adult life. During postoperative recovery and convalescence, rest is often essential and recovery may be seriously hampered by meddlesome therapeutics, unwise attention to intestinal elimination, or a disturbing nursing routine. The toxic adult is usually most carefully prepared for operation and the nontoxic one who is thoroughly convinced of the necessity for surgery is most cooperative. Children on the contrary often reach the operating room without adequate mental or physical preparation. Anxiety on the part of the parent excites fear in the child with consequent ill effects.[2] This can be avoided by quiet, sympathetic preliminary instruction of the parents combined with suitable sedation for the child. Except in emergency a blood and urine study should be made in addition to the general physical examination. If the coagulation time or hemoglobin is deficient the condition should be corrected by dietary regulation, calcium, blood transfusion, or such other treatment as is indicated. Intravenous solutions are valuable in supplying fluids and in building up an adequate carbohydrate reserve. If the urine contains acetone or diacetic acid only the most urgent surgery should be permitted and especial care should be taken to restore normal equilibrium by adequate amounts of fluid and carbohydrate. Careful preoperative preparation is rewarded in the great proportion of cases by a smooth and satisfactory postoperative recovery and an absence of psychic trauma with its inevitable subconscious scarring which may have far-reaching effects in later life.

ANESTHESIA

With the rapid development of various anesthetic agents the necessity of especially trained anesthetists is increasing. The trained anesthetist has much to offer the patient in diminished discomfort and reduced risk, and much to offer the surgeon in making operating conditions easier.[3] The anesthetist should be considered a consultant. He should have opportunity to study the patient and should determine the type of anesthesia which will best meet the requirements of both patient and surgeon. With the great variety of anesthetic agents at his disposal his position is not that of a minor technician.

The trained anesthetist is especially necessary and valuable for infants and children. In these little patients the volume of the tidal air is less, the zone of safety is narrower, and the metabolic processes are more rapid than in adults. The psychic effects also require especial consideration which often includes very definite preoperative advice to parents and carefully considered preoperative medication. While consideration of the fluid requirements of the body is important with all patients it is especially necessary when dealing with infants and children where dehydration and reduced nutrition produce serious consequences with startling rapidity. Unless the anesthetist is especially skilled in the use of the various anesthetic agents, ether is safest.[4] However, individualized and balanced anesthesia is equally as important and as definitely indicated as in the patient with toxic goiter. Night terrors, fear of the dark, and fear of falling asleep may at times be definitely traced to an anesthetic experience. Preparation for anesthesia should include building up adequate fluid and carbo-

hydrate reserve and regulation of the acid-alkali balance. This may require several days and may at times be the deciding factor in a good postoperative result. When fear has been instilled into the mind of a sensitive child by oversolicitous or unwise parents, the child's digestion and assimilation are often markedly impaired, even to the extent of vomiting and the development of either an acidosis or an alkalosis. Operations under such conditions have resulted in postoperative deaths directly traceable to improper preoperative preparation. Preoperative hospitalization, intravenous glucose and sedation may at times be necessary under these circumstances. With infants, regular feedings may be given to within three hours of the operation, but in older children an upset mental condition may delay emptying the stomach for as long as eight hours. The use of preoperative opiates and sedatives will vary in detail with the experience of the anesthetist; but a general rule should be that the child should reach the operating room in such a mental state that he will retain no unpleasant memory of the ordeal. In most instances sleep should be sufficiently deep that he will not be awakened by being moved gently or by the induction of the anesthetic. The barbiturates are excellent for this purpose and, in general, are to be preferred to morphine or its derivatives which often do not obliterate psychic effects and occasionally seem to increase nausea and vomiting.

Basal anesthesia by the intravenous or rectal use of the barbiturates is excellent, and although they are considered irreversible anesthetics because they cannot be withdrawn after introduction, the fact that they are broken down with extreme rapidity into harmless end products and that the depressing effect on the respiratory center can be counteracted by coramine, picrotoxin, and similar agents makes their effects definitely controllable. Avertin acts more slowly than the barbiturates and is eliminated more slowly, requiring at times as long as eighteen hours for complete disappearance. Its great advantages are the ease of administration by means of a procedure with which the average child is familiar, absence of unpleasant associations, and minimizing of psychic trauma. Against these are to be considered its slow detoxification[5] and the slight depletion of the glycogen reserve which is best met by increased preoperative carbohydrate intake and postoperative intravenous administration of glucose solution. Its use to obtain full anesthesia is unwise—fatalities having occurred which seem chargeable to it—but its value as a basal anesthetic is unquestionable. It should be given slowly, requiring at least ten minutes for the full amount to enter the bowel. The response of the patient during administration should be closely watched and if narcosis is unduly rapid or profound during the first few minutes the remainder of the solution should not be given, a respiratory stimulant should be used, and the supplemental anesthetic withheld until the peak effect of the avertin is past. If the bowel is not carefully prepared irregular absorption may occur and be responsible for variable depths of anesthesia. The best results are obtained if the lower bowel is thoroughly cleansed by enema on the evening previous to the operation and no enema given in the morning,[6] although when necessary the interval between cleansing and the instillation of the avertin may be as short as four or six hours.[7] Reports of respiratory depression and the necessity of stimulation are more frequent following rapid administration than when the slower method is used.

Experimental and clinical tests show that avertin does not cause delayed liver damage and that even when the liver had been purposely impaired in experimental animals by the excessive use of chloroform, additional damage by avertin is very slight and the total period of recovery from the chloroform poisoning is not increased.[8] One instance is reported of its use 22 times in less than ten weeks for repeated painful dressings without bad effect but with a gradually increasing tolerance until a dose of 225 mg. per kilo of body weight was required. Some degree of liver damage is produced by all anesthetics with the possible exception of cyclopropane, but it is usually negligible except with chloroform. It is most marked when there is cyanosis, regardless of the type of anesthetic, and therefore should be combated by the free administration of oxygen during anesthesia and the restoration of the glycogen reserve by intravenous carbohydrates postoperatively.

Of the barbiturates pentothal sodium is the most powerful and its careful use gives definitely controllable results. It is not considered as safe in children under ten years of age as in older patients because of the fact that since the air passages are smaller the molecular weight of the air remains unchanged and ventilation becomes inadequate.[9] Pentothal does not abolish throat reflexes and hence is unsatisfacory as a basal anesthetic preliminary to the use of the endotracheal technique. Unusual sensitivity to this drug may be indicated by sneezing, coughing, or hiccoughing early in the administration, and it should be stopped, continuing the anesthetic with some other agent. The barbiturates may be given by bowel, being administered in capsules the ends of which have been punctured, and while not as satisfactory as avertin they are at times more convenient.

It should be constantly borne in mind that avertin and the barbiturates are primarily of value in reducing psychic effects, are to be considered as basal—not total—anesthetics, and are respiratory depressants. The respiratory effects may be controlled by artificial respiration and by such drugs as coramine and picrotoxin. Picrotoxin may be given intravenously if immediate action is desirable,[10] using a dose of 5 mg. in water or normal saline in the strength of 2 mg. per cubic centimeter. Two and one-half cubic centimeters of this solution is given slowly and if no wakening effect is evident in twenty minutes this dose may be repeated. If not effective in an additional twenty minutes, the dose may be doubled, and smaller doses of 3 to 5 mg. may be added at intervals as necessary until the period of depression is over. Signs of wakening are improved depth and rate of respiration with improvement of muscle tone and circulation. If twitchings or minor convulsions occur they indicate an improvement in the depression of the central nervous system, and the picrotoxin should be discontinued until the signs of depression return. Picrotoxin should not be given in opium poisoning as it enhances the effect of morphine and seems to accelerate a fatal outcome. It has been used effectively in combination with pentothal in the ratio of 3 mg. to each grain of pentothal.[11]

A carefully planned, unobtrusive preparation for several days before operation with special attention to adequate vitamin intake, fluids, and carbohydrates, and proper mental attitude will do much to eliminate preoperative psychic disturbance and postoperative discomfort.[12] The best results are obtained when in addition to such preoperative care the anesthetist has the ability and opportunity to regulate the

preanesthetic medication and to vary the anesthetic procedure during the operation, changing the agent and method as necessary to meet the varying requirements of the patient and the surgeon. This constitutes what has been termed "balanced anesthesia,"[13] and may include any combinations of inhalation, intravenous, local, or rectal agents.

The use of cyclopropane is apparently steadily gaining favor with certain anesthetists who have the opportunity to study it carefully. It is particularly valuable when a high percentage of oxygen, or quiet respiration, is desirable; it does not affect liver function, and in such operations as spinal fusions, it minimizes shock. Since it is used in a closed system the cost may be as low as twenty-five cents per hour.[14] In spite of its many good points there are definite dangers. It is explosive and even though the closed system has been carefully inspected for leaks, no electrical apparatus should be allowed in the operating room. Respiration is so quiet that it is difficult to resist the temptation to use higher concentrations than are necessary and to hasten induction. Slight respiratory depression during induction may easily progress to respiratory arrest with irregular slow pulse, in which connection it is to be remembered that the use of adrenalin is contraindicated.[15] Early in the postoperative recovery period laryngeal spasm may occur with dilated pupils, circulatory depression, and cessation of respiration requiring forced inflation of the lungs.[4] Waters, who has had long laboratory and clinical experience with it, considers it still in the experimental stage but possessed of so many good qualities that continued clinical use by skilled and qualified observers is justifiable and desirable.

Under ordinary conditions spinal anesthesia is not considered advisable in children on account of their usual inability to appreciate the necessity of cooperation or the possible undesirable psychic effects. Certain children, however, on account of individual mental reactions, respond excellently and in others the pathologic condition makes the use of this type of anesthesia advisable. In such instances it becomes the method of choice. In operations usually associated with a considerable amount of surgical shock such as those involving the femur or in hip reconstruction, it is often wise to block the afferent impulses which may continue even during surgical anesthesia to produce reflex effects through the central nervous system.[4] It may also be used to advantage in operations where rather extensive intraabdominal manipulations may be anticipated or where the possible depressive effect of a general anesthetic seems dangerous. In small children and infants it should be given between the third and fourth lumbar spines at the rate of 1 c.c. of solution in three seconds. For pyloric stenosis 20 mg. dissolved in 1 c.c. of spinal fluid has been used, and in early childhood the general rule is to use 10 mg. for each year of age, dissolved in 3 c.c. of spinal fluid. Opinions differ as to the advisability of using spinal anesthesia in toxic cases such as pneumonia, tonsillitis, and other acute infections. In one series of 53 cases, however, it was considered the method of choice in poor surgical risks such as surgery in the presence of measles, influenza, bronchitis, tonsillitis, pulmonary tuberculosis, and pneumonia.[16] The conditions requiring surgery included appendicitis, strangulated hernia, intussusception, twisted ovarian cyst, ruptured spleen, osteomyelitis, fractures, and cryptorchidism. Nausea and vomiting from psychic reaction occurred in five cases but

preoperative morphine was not considered advisable. In these desperately ill children all possible precautions against accidents should be taken and such resuscitative measures as coramine, posture, and intravenous 50 per cent glucose should be used upon the first indications of emergency. Labat administered the anesthetic in most instances, obtaining perfect anesthesia in all but five cases, and in two the anesthesia extended from the scalp to the toes without respiratory embarrassment.

It would appear that while spinal anesthesia may be indicated in some cases of poor pediatric surgical risks the indications should be definite and most carefully considered and that in less experienced hands than those of Labat its use may not be attended by such favorable results.

BURNS

The problem of controlling secondary infection of burned areas is always difficult. A burn is sterile at first, but, as it is usually necessary to give antishock measures precedence over all others, bacterial contamination of denuded areas during this period is almost inevitable. The bacterial flora which is mixed at first gradually changes to one which in most instances is predominantly hemolytic streptococcus. It is in this stage that treatment by gentian violet has its greatest value because of the high specificity of the aniline dyes for the coccal forms of bacteria.

A combination of acriviolet and brilliant green is reported to be the most powerful combination against the gram-positive bacteria which does not injure living tissue cells, and it is also highly effective against the gram-negative bacteria.[17] After preliminary treatment for shock an atomizer is used to spray the burned area hourly for a day. A rather tough flexible crust forms rapidly sterilizing the area as it seals, preventing fluid loss and protecting nerve endings in the same manner as other substances used for this purpose. No cleaning of the area is necessary unless there is gross contamination. If localized areas of infection persist beneath the crust, they should be uncovered, dried with sterile gauze, and the dye should be reapplied except when the areas are extensive; then they may be treated by removal of the crust and hourly changes of sterile normal saline compresses. This treatment so reduces the infection within a few hours that the dye may be reapplied. Even in third degree burns there are often epithelial cells at the bases of the hair follicles which soon form islands of regenerating skin with the production of a surface which is fairly soft with a minimum of scar contraction.

Aside from this, little has appeared in the literature of the past year which differs from the methods already noted in these reviews. The great value of crust formation is widely recognized and accepted, particularly the use of 10 per cent tannic acid followed by 10 per cent silver nitrate,[18] as described by Bettman. The effectiveness of this crust, as well as that of the ferric chloride method, is such that appendectomy has been performed through an incision directly through the crust with normal uncomplicated healing.[19]

In the secondary treatment of burned areas skin grafting is of prime importance to minimize contractures, to combat absorption, and generally to reduce systemic symptoms. Preliminary to grafting, granulating areas may be prepared by daily washing with equal parts of tincture of green soap and hydrogen peroxide followed by any non-

irritant mildly antiseptic dressing.[20] For sluggish granulations cod liver oil dressings or Bettman's scarlet R gauze may be used to advantage. Small Reverdin grafts are of value in obtaining quick covering of granulating areas which may still have some infection. They form a covering which, however, must usually be considered temporary because of poor cosmetic appearance, each graft becoming surrounded by scar which often requires a long time to become soft and pliable. The treatment of burn scars requires the patience, ingenuity, and resourcefulness of the plastic surgeon combined with the willingness of the patient to submit to a prolonged course of operative and nonoperative procedures.

ABDOMINAL CONDITIONS

Acute peritonitis is considered primary when it develops without evidence of preexisting abdominal inflammation.[21] It is usually hematogenous following an acute upper respiratory infection and may be streptococcic or pneumococcic. Direct infection by the pneumococcus may occur through the fallopian tubes, and by the streptococcus from a suppurating mesenteric gland during the course of scarlet fever.[22] There is severe abdominal pain and tenderness with generalized rigidity and the development of distention. Vomiting is early and persistent, usually preceding the pain, and there may be hiccoughing and diarrhea. Cessation of vomiting indicates localization of the peritonitis. The leucocyte count is high—20,000 or more at first—with a polymorphonuclear percentage in excess of 85 and a marked increase of the immature forms as shown by a shift to the left in the Schilling count. The sedimentation rate is increased—a distinction from acute appendicitis in which it is normal. Abdominal puncture is valuable in determining the type of infection but if negative does not rule out peritonitis. The presence of organisms of the colon group indicates a perforated appendix, as puncture of a distended loop of bowel is almost impossible with ordinary care. Laparotomy is useless during the stage of spreading infection, regardless of the type of organism, as streptococcic peritonitis does not tend to localize, and the prognosis is particularly poor, while pneumococcic and colon peritonitis will often become localized if given time. The operative mortality in the pneumococcus type is 90 per cent if the operation is performed during the first few days and only 7 per cent if operation is delayed two or three weeks. Conservative treatment yields the best results in all types of general peritonitis. Repeated small blood transfusions are often valuable, and specific antiserums or convalescent serum may be tried. The usual treatment consists of the Fowler position, heat to the abdomen, continuous suction syphon drainage of the upper intestine by means of the nasal duodenal tube, rectal irrigation, and intravenous administration of fluids such as saline, glucose, and Hartmann's solution. Pitressin or similar peristaltic stimulants are occasionally of value.

Bile peritonitis is a rare condition occasionally occurring in infants as the result of some congenital abnormality of the biliary system, such as atresia of the common duct or following obstruction of the common duct by inspissated bile.[23] Marked dilatation of the common duct produces a condition which is known as choledochus cyst.[24] The symptoms are increasing size of the upper abdomen and gradually developing jaundice. There is usually pain, and there may be fever

and weakness. The symptoms are not distinctive, and diagnosis is difficult. Rupture of such a cyst causes bile peritonitis. In the infant type the peritonitis is aseptic and mild, and jaundice does not develop early. The initial symptoms are vague: the child is restless and does not gain weight well, the stool is usually acholic, and there may be bile in the urine. A significant sign is swelling of the scrotum. Aspiration is a valuable diagnostic measure and may be of therapeutic value to relieve symptoms due to abdominal distention and pressure. The treatment is suture of the duct, anastomosis with the duodenum, or simple drainage, depending upon the conditions found.

Another rather rare condition which is often suddenly fatal is adrenal hemorrhage, which may occur during the course of some severe infection.[25] It is suggested that the circulating bacterial toxins cause marked permeability of the walls of the blood vessels of the adrenals, as there are often associated petechial skin hemorrhages. Suggestive symptoms are high fever and circulatory collapse; there are, however, no characteristic signs or tests. Treatment by evacuation of the clots from the adrenals seems to ignore the causative factor and would add surgical trauma to an already severe toxemia. Surgery under such conditions would appear to be a doubtful gesture rather than a procedure based upon sound judgment and understanding of the underlying pathologic conditions.

In a careful study of idiopathic thrombocytopenic purpura at the spleen clinic of Columbia University covering ten operative and eleven nonoperative cases, it was concluded that although splenectomy is a major operative procedure, the results justify the risk.[26] Excellent results were three times as frequent as poor in operative cases, and poor results were five times as frequent as good in the nonoperative. One death occurred among the operative cases during a fulminating recurrence eighteen months after the operation, but severe postoperative complications were rather frequent. A sharp reduction in mortality in recent years is probably due to improved diagnosis and preoperative preparation, better surgical technic, and more careful choice of anesthetic. The condition is more common during the first decade. Skin purpura and hemorrhages of some type were common, and the spleen was palpable in about half the cases. The platelet count was low, bleeding time prolonged, clotting time normal, tourniquet test positive, and leucocyte and differential counts were within normal limits. Clot retraction was usually delayed. These are the usual symptoms and signs the importance of which has repeatedly been stressed and which must be present if surgery is to be productive of the best results. Preoperative transfusions may be of value, but the effect is transient, and the rather alarming hemorrhage which may occur during operation stops spectacularly as soon as the splenic blood vessels are clamped. Transfusion at this juncture or immediately after the operation gives more lasting effects. The presence of accessory spleens or the incomplete removal of all splenic tissue on account of dense adhesions may account for failure to obtain a satisfactory result.[27] When thrombocytopenia and hemorrhages are the prominent symptoms, these have been satisfactorily controlled by roentgenotherapy over the spleen. If the destruction of platelets in the spleen is due to a circulating toxin, the function of the spleen is lowered temporarily by this treatment until the toxemia is overcome, but, if the destruction is due to an endocrine disorder of the spleen itself, intensive

radiation may be necessary to render it permanently functionless.[28] Extreme nicety of judgment will be required to determine the dosage of radiation necessary to produce the desired degree of impaired function during the elimination of the toxic factors, and, unless the return of such factors can be definitely controlled, recurrence would seem probable. The production of extensive perisplenic adhesions by roentgenotherapy has been noted by some observers and introduces a complicating factor if subsequent surgery should become necessary.

Traumatic diaphragmatic hernia is a condition which must be considered following any type of violent injury, and it is becoming increasingly frequent on account of automobile accidents. The symptoms are usually masked at first by shock but later may appear as circulatory, respiratory, and gastrointestinal disturbances, such as dyspnea, palpitation, feeling of suffocation when lying down, pain in the chest which may be referred to the neck and shoulder, cyanosis, cough, indigestion which may suggest ulcer, nausea, and vomiting. Symptoms of obstruction develop when there is volvulus or strangulation which may occur at any time. The physical findings often vary with change of position. There are intestinal sounds in the thorax, displacement of the heart, immobility of the affected side, and asymmetry.[29] The roentgenologic findings are diagnostic.[30] The congenital type is differentiated from the traumatic by the normal fixation of the cecum in the latter. In the former there is usually incomplete rotation, the colon, cecum and appendix are often in the chest, and are easily shown by barium or the presence of gas. In the congenital type the diaphragmatic opening may be large, and the edges of it may be noted as a constriction in the barium shadow. Hernia through the hiatus is rare in children, and the stomach is usually in the abdomen in the erect position. Roentgenograms in various positions are often of great assistance in diagnosis, especially the inverted position in infants after administration of a small amount of barium. With true thoracic stomach the esophagus is short and enters the tip of a conical fundus. It is to be carefully differentiated from diaphragmatic hernia as it is not amenable to surgery. Eventration is a term occasionally applied to a condition characterized by a very high, thin diaphragm. It is often hard to see the shadow or motion of such a diaphragm and at times it cannot be differentiated roentgenologically from diaphragmatic hernia.

Intraabdominal hernia occasionally occurs through a congenital defect in the mesocolon.[31] The defect is usually found in the mesentery of the ascending colon, and the symptoms are the usual ones of obstruction or strangulation. Early operation with reduction of the hernia and repair of the opening is essential, as prognosis is poor if impairment of the circulation of the bowel has occurred. It is better to do an exploratory laparotomy than to lose valuable time in attempting a fine differential diagnosis.

Symptoms and signs of intestinal obstruction in infants are caused by comparatively few conditions. These are, pyloric stenosis, intestinal atresia, and anomalies of intestinal rotation or fixation.[32] The symptom common to all of these is persistent vomiting becoming violent and projectile. If a high obstruction such as pyloric stenosis. duodenal atresia, or duodenal stenosis is suspected, a small amount of a thin barium suspension may be of great assistance even though it is advisable in instances of complete obstruction to remove it by

lavage before operation. An obstruction other than pyloric stenosis may be suspected if the vomiting begins during the first week of life, if the child is female, if there are other congenital abnormalities, and if there is blood or bile in the vomitus. The presence of a normal amount of bile in the meconium indicates a pyloric or high duodenal obstruction, but a small amount of bile coloring cannot be relied upon, as it may reach the lower bowel through the blood or tissues or because of an anomaly of the biliary ducts. Intestinal atresia may be multiple, a condition which cannot be determined before operation and for which little can be done, as anastomosis is preferable to enterostomy which is not well tolerated. If atresia is found, fluid or air may be injected into the collapsed bowel distal to the atresia in an attempt to determine whether there is another similar obstruction lower. There is a high mortality even under favorable conditions. If the obstruction is due to an anomaly of descent or rotation, a thorough understanding of the normal process and conditions is essential, and an excellent presentation may be found in this reference. This should not be condensed into an abstract as valuable details would necessarily be omitted and a full inclusion would require too much space. At operation the anomaly should be derotated or untangled, as any type of anastomosis is inadvisable. Exposure of the root of the mesentery by detaching the ascending and transverse colon from the parietal wall and rotating them toward the midline is usually necessary. Extreme gentleness in handling these tissues rather than speed is emphasized, as the preoperative condition can usually be satisfactorily improved by intravenous or subcutaneous fluids. It is pertinently and pointedly noted that "the flashy, speedy, rough surgeon will not do well in these cases."

Mesenteric adenitis occurs in later rather than early childhood although it has been reported as early as three years of age.[33, 34] The symptoms are such that it is difficult to differentiate it from appendicitis, and laparotomy is usually obligatory. If there is no history of previous illness and if vomiting is not persistent, the inflamed glands are more likely to be found in the mesentery and to be pearly gray in color, while, if there have been repeated attacks with little or no vomiting, they are more likely to be retroperitoneal and of a reddish pink color. They may be removed for study without danger of peritoneal irritation as cultures are almost invariably negative. This is such a constant finding that the theory has been advanced that the condition is due to a filtrable virus. The probability is, however, that the source of the infection is the appendix, because of the fact that the attacks cease after the appendix is removed even though little appendiceal involvement can be found at the time of operation. The pain is rather severe and constant but lacks the usual cramping or recurrent character usually found in appendicitis, and the tenderness is more apt to be vague and general, with only occasional slight rigidity. The pulse, temperature, respiration, blood count, and urine give no practical points of differentiation.

Ovarian cysts occur in later childhood. They rarely cause symptoms until a complication such as rupture or torsion of the pedicle occurs. The symptoms indicating rupture are sudden severe abdominal pain of perhaps two hours' duration with normal temperature and leucocyte count.[35] There may be complete disappearance of symptoms followed by recurrence in a few weeks. Pallor of the mucous membranes sug-

gests hemorrhage following the rupture. Torsion of the pedicle, if gradual or chronic, causes a painless enlargement of the abdomen.[36] Since more sudden onset causes rather severe pain which if right-sided is usually mistaken for appendicitis, this condition should be borne in mind when at operation the condition of the appendix does not seem to warrant the symptoms. The pain may be referred to the lateral aspect of the thigh or to the lumbar region from which it radiates to the perineum. Sudden symptoms of shock indicate strangulation or gangrene, which is a surgical emergency. The condition may be confused with intestinal obstruction, mesenteric adenitis, or ureteral calculus, as well as appendicitis. Rectal examination and roentgenograms before and after emptying the bladder are of diagnostic value.[37]

As has been often emphasized in these Reviews, the treatment of peritonitis is not that of appendicitis even though the peritonitis be caused by a ruptured appendix. Conservative treatment of peritonitis results in a much lower mortality than the operative. It consists essentially of physiologic rest for the alimentary tract to permit localization, with later surgical drainage at the optimum time.[38] Gas and secretions in the upper intestinal tract are removed by continuous suction syphon drainage through an indwelling nasal duodenal tube, minimizing or preventing the serious and often fatal train of events due to pressure on the vessels and nerves of the intestinal wall by excessive distention. The accumulation of gas in the lower portions of the small bowel is reduced by adequate doses of morphine which increases intestinal tone, and by inhalations of oxygen in concentration of at least 95 per cent which removes nitrogen from the blood and so favors passage of the intraintestinal nitrogen into the circulation. Peristaltic drugs are contraindicated during the period of localization as is also rectal administration of fluid, which stimulates peristalsis. Fluid and electrolytes are given intravenously at a slow rate over long periods, using glucose, Hartmann's and saline solutions, as the condition demands. The appearance of edema indicates chloride retention, and all sodium chloride should be discontinued; glucose solutions should be used if fluids are necessary. The adequacy of the fluid intake is judged by the urinary output, as the kidneys excrete only the fluid which remains after the body requirements are satisfied—900 c.c. to 2,100 c.c. per day being adequate for a child, depending upon the body weight. Fowler's position favors the movement of gas to the upper portions of the intestine and stomach where it can be reached by the duodenal tube. Heat to the abdomen is considered beneficial because of its derivative effect on the circulation, a vasodilation of the somatic area producing a vasoconstriction of the splanchnic. Nothing should be given by mouth, although in our experience we have found that fluids may be begun cautiously while the duodenal tube is still in place. This treatment should be continued as long as there is improvement, usually about a week; in most instances there are relief and disappearance of the peritoneal symptoms, with localized abscess in only about one-fourth of the cases. The earliest evidence of improvement can be detected by use of the Schilling count,[39] a decrease in the shift to the left indicating a return of reactive ability before clinical improvement is noted.

Interpretation of the pathologic condition of the appendix during the acute or subacute stage is facilitated by the use of a hemogram which has been carefully worked out by means of successive Schilling

counts and the development of various indices.[40] This requires practice in preparing the slides, experience in interpreting the counts, and a reduction in the error attributable to the personal equation, but permits a surprisingly accurate diagnosis of the pathologic condition of the appendix in about 90 per cent of cases, and is of definite value in prognosis. It is not, however, of great assistance in differential diagnosis.

The necessity of operation early in the course of acute appendicitis is being constantly stressed and rightly so, as the lowest mortality and morbidity follow removal of the appendix during the first twenty-four hours. In the first half of the second twenty-four hours the operative mortality rises to 2 or 3 per cent, on the third day it is about 10 per cent, and on the fourth and fifth days it is higher.[41] For this reason the conservative treatment is advisable in those patients seen on the third day or later. It is a distressing fact that such patients frequently have a large group of friends or relatives who have heard of the necessity for early operation and who consequently believe that operation offers the only hope of recovery regardless of the stage of the disease. These well-meaning persons demand that something be done and do not differentiate between doing something for the patient and doing something to him. They place a tremendous strain upon the judgment, patience, and tact of the surgeon, and it is often far more difficult to refrain from operating than to operate. The faith of the laity in surgery unfortunately makes it much easier to believe that a postoperative death has occurred in spite of the operation and that every effort has been made to save the little patient rather than that the loss of the child has been due to a poorly timed operation. The demand for action is more often for the relief of the mental condition of the family than for the relief of the physical condition of the patient. Why not turn this faith in surgery to the advantage of children by prophylactic appendectomy, not to prevent appendicitis but to prevent the peritonitis which so frequently follows an early perforation. The value of prophylaxis against contagious disease has become well recognized, and the mortality rate of contagious disease is far below that of appendiceal peritonitis. Many factors are of course involved in the acceptance of surgical prophylaxis: a fear of, as well as faith in, surgery; the question of judgment as to general physical condition; the hospital and absence from home; financial considerations; the skill of the operator; and the placing of responsibility.

A great service may be done for children by recognition of appendicular colic[42] and of the improvement which follows appendectomy in these children who are rarely strong and robust. The symptoms are colicky pain, nausea and vomiting, very slight rise in temperature and pulse, and very slight variation from the normal blood picture. The pain is definite and rhythmic, but rarely localized in the right lower quadrant. The attacks seldom last more than a few hours. Such a syndrome is strongly suggestive of partial appendiceal obstruction, either by a band, kink, or fecalith, and sudden perforation may occur during one of the attacks.

It is interesting to note a report of nine cases of appendicitis occurring during measles and the opinion that there may be a relationship between appendicitis and the visceral symptoms of measles.[43] Such a view seems most reasonable. Abdominal symptoms under such

conditions deserve careful study, and, if appendicitis seems probable, operation is indicated in spite of the presence of measles.

In infants the four surgical conditions of the alimentary tract most frequently encountered are pyloric stenosis, intestinal atresia, volvulus, and intussusception.[44] These are all noninflammatory and obstructive and are related in various ways to early development and adjustment.

In pyloric stenosis the cardinal signs and symptoms are projectile vomiting, scanty stool, loss of weight, dehydration, visible peristalsis, and tumor. The supplemental use of roentgenograms in diagnosis is neither necessary nor desirable, but it may be of assistance or of confirmatory value until experience has been acquired. Careful preoperative treatment of dehydration is essential to good postoperative recovery. Blood transfusion is ordinarily not indicated as the blood picture is that of condensation which is best met by the administration of saline solution or glucose in saline solution.[45] The operative errors to be avoided are failure to sever all circular fibers of the pylorus, perforation of the mucosa, and insecure closure of the abdominal incision. Loss of body heat on the operating table is to be avoided, especially that due to the refrigerating action of volatile solutions used for skin preparation. A transverse skin incision above the level of the liver edge with lateral retraction of the rectus is often of value in facilitating a secure closure on account of the unimpaired rectus and the trap-door action of the liver edge.[46] Postoperatively, fluid requirements should be promptly met, and nutritional requirements are such that the patient should be returned to full diet in less than forty-eight hours, using small frequent feedings and returning to the four-hour interval in not less than two weeks.

Intestinal atresia and volvulus present the usual signs of intestinal obstruction. In the former there is absence of normal stools, and the meconium does not contain keratinized epithelial cells. The bowel usually perforates a few inches from the obstruction on the fifth or sixth day; therefore operation not later than the fourth day is indicated. With volvulus there is rarely much distention because the pressure is usually on the duodenum.

Recovery from intussusception is directly proportional to the duration of the condition before operation. Reduction by enema, while possible in some cases, is not advised because those patients relieved by this method are also the best surgical risks, and, if the enema treatment is unsuccessful, there is unnecessary shock, loss of time, and increased mortality in patients in whom the margin of safety is already narrow. Great patience and gentleness are requisite in operative manipulations of the bowel. To reduce the last few inches it may be necessary to split the muscular wall—such procedure being preferable to resection which is attended by a high mortality. If resection should be necessary on account of gangrene, a double-barreled enterostomy should be done with later secondary closure. Operative measures to prevent recurrence add a factor of danger, their effectiveness is questionable, and experience in 431 cases indicates that they are unnecessary, as there were less than 2 per cent of recurrences in this series with no mortality in the recurrent cases.

A clear understanding of the factors involved in intestinal obstruction is essential for rational treatment.[47] Distention following obstruction is both gaseous and fluid. Endogenous fluids consisting of the various secretions of the alimentary tract amount to 7,000 c.c. per

day in the adult, and 70 per cent of the gas is made up of swallowed air. Thinning of the bowel wall by distention interferes with circulation, capillary rupture and hemorrhage occurring when the venous return is impeded, and toxic absorption, gangrene, and perforation following arterial obstruction. The important diagnostic points are borborygmus and intermittent cramping pains. These indicate intestinal colic which may be due to enterocolitis but, when accompanied by distention, spell obstruction. Roentgenograms are a valuable aid in showing liquid levels and the location of the distended intestinal loops, and they should be made in various positions. In simple obstruction decompression is essential, either surgical or nonsurgical. In most instances of upper intestinal distention suction siphon drainage by nasal duodenal tube is effective, but, if improvement does not occur or if the obstruction is evidently low, surgical decompression is indicated. If surgery is necessary, manipulation and anastomosis are to be avoided particularly in late obstruction as they are not well tolerated, and only the simplest enterostomy should be done. In early simple obstruction a careful search for and release of the obstructing mechanism is advisable and is attended by only a moderate increase of risk. If signs indicate a strangulation obstruction, nonsurgical decompression is contraindicated, and operation is obligatory with the possible exception of mesenteric thrombosis. The operative risk is great and the mortality high. Loss of fluid from the upper intestinal tract whether it occurs through a fistula, enterostomy, or duodenal tube may result in alkalosis because of the relative excess of chlorine ions over basic ions, and the blood will show a marked decrease in the plasma chlorides.[48] If, however, the fluid loss is from the more distal portion of the small intestine, acidosis is more likely to occur because of the more extensive depletion of the basic ions. In the former instance the acid requirements may be met by the administration of normal saline, but in the latter a combination of sodium chloride and sodium bicarbonate is indicated since the use of saline solution alone would supply a fixed acid to an organism which already possesses acid in excess. A careful check of the acid-alkali balance and a determination of the body requirements as regards electrolytes are advisable in all prolonged cases of intestinal fistula or drainage; attention to the maintenance of this balance may well be the deciding factor in recovery.

Unusual types of intussusception occasionally occur. Chronic or frequently recurring intussusception of six weeks' duration combined with a retrograde intussusception of the descending colon is reported.[49] There were the usual symptoms but not of sufficient severity at first to bring the child under medical observation. Jejunal intussusception is found more frequently in later childhood and adult life than in infancy.[50] Blood appears in the stool in only about 25 per cent of the cases, and an abdominal tumor is not always palpable. The history may be of chronic abdominal pain, occasional vomiting, epigastric distress, and constipation; or acute abdominal pain, repeated vomiting, distention, tenderness and rigidity, in some instances the pinching of the mesentery being so severe as to give the picture of peritoneal shock.

Segmental neuralgia is a term which has been applied to a condition which may cause confusion in the diagnosis of the cause of abdominal pain in older children.[51] It usually occurs in the puberty or prepuberty period following some infection, and runs a self-limited course

of two to four weeks. Vomiting occasionally accompanies the onset of the pain, but rigidity is rare. The pain is usually tingling or burning, occasionally severe or paroxysmal, and careful examination will in most instances demonstrate that it is in the abdominal wall rather than intraabdominal. There is often tenderness to deep pressure along the course of the affected sensory nerve and in the paravertebral region. In the area of distribution of the sensory nerve there are sharply limited hyperalgesia, hyperesthesia, and irregular pain reactions to pressure. Variable amounts of relief may be obtained by heat, counterirritants, and sedatives, and removal of local foci of infection is advised. Recurrences are rare. The condition is thought to be due to toxic irritation of nerve roots or ganglions, possibly by a neurotrophic virus with special predilection for these tissues. Although rarely seen, this condition is to be considered in the occasionally puzzling conditions encountered in this rather unstable period of childhood.

Meckel's diverticulum should be looked for whenever circumstances permit and removed whenever found. Like the appendix it is dangerous not so much on account of acute inflammation as for the sequelae. Perforation and the resulting peritonitis are particularly fatal;[52] and umbilical hernia and malignancy are serious complications in adult life.[53] Perforation occurs in the mucosa of the ileum immediately adjacent to the usually found ectopic gastric mucosa. There is frequently a history of blood in the stool, and the onset is with nausea, vomiting, and colicky pain located vaguely about the umbilicus, later shifting slightly to the right of the midline of the lower abdomen, and followed shortly by the signs and symptoms of peritonitis. Fluoroscopy in the erect position may show a gas bubble beneath the diaphragm. In searching for a diverticulum, it is to be borne in mind that the diverticulum may lie between the leaves of the mesentery.

Imperforate anus is due to atresia or malformation of the lower end of the alimentary tract and may vary greatly depending upon the position of the anal dimple and rectal pouch.[54] The rectal pouch may be separated from the anal dimple by a thin membrane which bulges with straining, or it may lie several inches higher. When the distance between the ischial tuberosities is abnormally short, it is evidence that the rectal pouch is not in the pelvis. If there is no distinct bulging, the position of the blind end of the bowel should be accurately determined by a roentgenogram in the inverted position after sufficient time has elapsed for gas to be present in the bowel. Simple incision is indicated if there is marked bulging, but blind exploration with a needle or trocar is dangerous because there may be a peritoneal culdesac low in the pelvis. If the rectal pouch is within an inch of the skin, open dissection is the only safe method, and the end of the bowel should be identified under direct vision. This may be done under local anesthesia. The mucosa should be sutured to skin flaps without tension, and no tube should be introduced because of the danger of pressure necrosis. After healing, daily gentle dilatation is necessary to prevent scar contraction. Colostomy is necessary if distention develops or if the end of the bowel is high, and this should be done by the fourth or fifth day.

Associated with imperforate anus may be a fistulous opening into the vagina, urethra, or bladder, and careful search should be made for such a condition. Hardened meconium may so obstruct an other-

wise adequate rectovaginal opening as to cause distention.[55] If the vaginal opening is large enough to permit normal movements, surgery may be delayed four to six years. The internal and external sphincters usually develop in connection with the perineum and not with the bowel, a definite anal pit being good evidence of the presence of a sphincter. Control may develop about a rectovaginal opening, and, if so, it may be advisable to leave it rather than to run the risk of lack of control with transplantation to the normal position. With an incontinent vaginal opening, however, transplantation is indicated. Transplantation through two transverse openings is preferable to the usual operation through a median incision because the perineal body is preserved, there is less tendency to return to the former position, and the formation of adequate skin flaps is possible.

Peptic ulcer is occasionally encountered in children,[56] more frequently in later childhood than in infancy. In the older children the symptoms of repeated mild gastrointestinal disturbance, epigastric pain, distress after meals, and occasional nausea and vomiting are similar to those occurring in adults. The condition usually yields to medical treatment, but surgery is occasionally necessary if there is repeated finding of blood in the stool, the child fails to improve, and a careful gastrointestinal study shows the presence of the ulcer.

Regional ileitis, usually of the terminal ileum, is a condition of unknown etiology which is occasionally found when a diagnosis of appendicitis has been made.[57] The two are often indistinguishable before the abdomen is opened. There is a marked hyperemic thickening of the bowel wall suggestive of a granulomatous inflammation, and in some instances the appendix shows little or no involvement. In the more advanced stages the symptoms suggest partial intestinal obstruction, and a roentgenologic study may show a thin trickle of the opaque medium passing through the affected area—the so-called "string test." Perforation and fistula may occur in the later stages when there are marked thickening and constriction. Treatment of all types is rather unsatisfactory, and the less surgery the better. Appendectomy except in the presence of acute appendicitis is unwise, and, when it is necessary, the stump should not be inverted. Resection is dangerous on account of the great vascularity and friability of tissues. Enterocolostomy or drainage of localized abscesses may be necessary at times, but in general the prognosis is unfavorable.

The use of apple powder in the treatment of intestinal disorders has been steadily increasing during the past few years, its value apparently being in its detoxifying properties and the physiologic regulation of peristalsis.[58] It has been used mainly in the treatment of diarrheas, but recently its properties have been found of value in the preoperative preparation of surgical patients.[59] In the study reported, raw apple pulp was used, the method being to feed large quantities of raw apple upon an empty stomach and to allow time for the pulp to pass into the bowel before adding other food. Adults are directed to eat at least fifteen apples, which must be finely chewed, each day for two days before operation. The addition of high protein food is contraindicated as it may completely neutralize the beneficial effects of the apple pulp. The results claimed are absence of postoperative nausea, colic, and distention, the bowel being collapsed during operation. Peristalsis is markedly inhibited, and the bowel apparently lies dormant for several days when filled with the pulp. When movements

are finally induced, there may be rather severe abdominal pain. The application of this method of preoperative preparation to surgical conditions of children is not at once apparent, as it requires definite effort to consume the required amount of pulp, and entirely satisfactory postoperative recovery is usual if care is exercised in preparation and after treatment. As a means however of detoxifying the bowel contents and regulation of peristalsis some time previous to operation, the use of apple either as powder or pulp deserves continued study.

ANGIOMA

Angiomas of the face, always disfiguring even though small, are a source of much concern to parents. In the great majority of instances removal is possible, and the final results excellent, but treatment should be under the direction either of a dermatologist or other physician especially skilled in the treatment of these conditions. Various methods of treatment are used, depending upon the type of lesion, age of the patient, and the experience of the operator.[60] Bad results following irradiation, such as excessive scarring or arrested development of adjacent structures, are usually due to improper use of the agent. Scarring may necessitate excision and skin grafting at a later date. Angiomas are more common in premature infants and those of low birth weight than in normal ones and appear twice as frequently in females as in males.[61]

The superficial angioma simplex and the deeper cavernous type may not be present at birth but appear soon after and increase rapidly in size for several months. Those of the port-wine type remain the same size. Treatment should be begun in infancy or early childhood to obtain the best results and to avoid serious social and economic handicaps later in life.[62] During the first three months compression by pads, adhesive plaster or collodion is occasionally effective. In the superficial forms and the telangiectases treatment with the Kromayer light or carefully controlled carbon dioxide snow is usually excellent. Surgical excision requires much less time and is indicated when the location and size of the lesion admit of obtaining an inconspicuous lineal scar, and is preferable in hair-bearing areas where irradiation might kill the adjacent hair follicles. Cauterizing agents may cause vascular inflammatory reactions, and sclerosing solutions, sloughing. Radium requires expert care and attention, especially when used in the vicinity of important organs, but, when so used, it leaves no scar and is the treatment of choice for both the simple and cavernous forms. Treatment should be begun during the first year, never later than the third year, and immediately if the size is increasing. When expert supervision of radium is not available, excellent results may be obtained by the Kromayer light, carbon dioxide snow, excision, or electrodesiccation. Angiomas may be injured or infected, and, while the resulting ulceration may destroy them, the scarring could have been avoided by proper treatment. They never become malignant. The very deep cavernous type may involve muscle or even bone and is best treated by excision or injection. The small spider nevus occasionally seen on the faces of infants may disappear but is likely to persist. It is destroyed without scarring by electrolysis or carbon dioxide snow, but electrodesiccation is likely to result in scarring.

Flat port-wine marks of small size may be removed by repeated strong applications of carbon dioxide snow or water-cooled ultra-

violet light, but a scar remains, which however may be preferable to the disfiguring marks. If the lesion is extensive, it is best left untreated. The pigmented nevus or mole is usually flat at first but may later become elevated. Those which have the appearance of normal skin but are brown or black are considered benign, while those hairless ones of a slaty, bluish color are potentially dangerous, as carcinoma may develop following injury or irritation. The benign type may be removed by electrocoagulation or carbon dioxide snow, but the potentially dangerous type requires wide excision with the diathermy knife down to the underlying muscle.

RESPIRATORY TRACT

Dyspnea and cyanosis in the newborn infant which persist or increase in spite of aspiration of mucus from the throat may be due to congenital stenosis of the larynx, failure of the glottis to open sufficiently, or a partial diaphragm below the vocal cords.[63] Relief may be obtained by tracheotomy, but it is probable that it will be necessary to continue the use of the tube for months or perhaps years until growth and development of the larynx and trachea have taken place or until the cause of the stenosis can be treated surgically.

Laryngeal symptoms in the newborn may also be due to paralysis from instrumental trauma or excessive traction during prolonged labor.[64] Occasionally an inspiratory crow may indicate an epiglottic deformity caused by rickets or underdevelopment, in which case the deformity will disappear with improved nutrition. During childhood suddenly developing laryngeal symptoms and dyspnea may require emergency tracheotomy, but, if there is time, a careful history is always valuable. If the attack occurred while the child was running with something in his mouth or while he was eating, a foreign body may be lodged in the larynx or trachea or may have been coughed out, leaving a traumatized mucosa. Secretions may be spilled over into the larynx from the esophagus where the foreign body may be lodged. Repeated attacks of hoarseness or croupiness, especially at night over a period of weeks or months, may indicate a new growth on the vocal cords. If possible, diagnosis by direct laryngoscopy is preferable to inferential diagnosis and permits intelligently directed treatment.

In infants obstruction to respiration may be nasal as a result of a dislocation of the lower edge of the cartilaginous nasal septum during passage of the head through the birth canal or later in infancy to a blow on the nose.[65] This removes part of the normal support and allows the tip to drop. Inspection will usually show the edge of the cartilage presenting under the mucosa or it may be felt beneath the skin of the columella. The dislocation should be reduced promptly to avoid subsequent deformity and interference with respiration.

The removal of small foreign bodies from the lungs is extremely difficult on account of their tendency to gravitate to the periphery of the lowest portions of the bronchial tree. A special costophrenic bronchoscope has been devised for this purpose, but the technic is difficult and requires the services of a bronchoscopist and a roentgenologist who is skilled in the use of the double plane fluoroscope.[66] Pins are the foreign bodies most frequently requiring this apparatus, and any method by which their removal is facilitated will reduce the incidence of lung abscess in children.

Lung abscess is being reported more frequently than formerly, but it is difficult to determine whether the increase is actual and due to more tonsillectomies or only apparent because of improved methods of diagnosis.[67] The condition is serious, requires long hospitalization, and tends to become chronic. The onset is similar to that of an acute infection with high fever, chills, pain, cough, and leucocytosis, followed in a short time by distinct localization, the position of which can be determined by roentgenography. If the abscess ruptures into a main bronchus soon after localization, it may heal completely within a month. If it ruptures through the pleura, it forms a typical empyema. Treatment by postural drainage, general supportive measures, and bronchoscopic aspiration is effective in some cases, but, if improvement ceases, a two-stage thoracotomy may be necessary to evacuate the pus externally. Lung abscess is differentiated from pulmonary gangrene by the presence of spirochetes, fusiform bacilli, and extremely foul odor in the latter condition.[68] Gangrene is usually due to tonsillectomy when the tonsils or the oral cavity are infected by these organisms. Such infection should be eliminated by vigorous preoperative treatment. Differentiation between gangrene and an abscess is necessary since the treatment is radically different—gangrene being treated by intensive intravenous arsenical medication. If cavity formation occurs in spite of this treatment, thoracotomy may be necessary, but the specific medication should be continued to minimize the chance of infection of the chest wall. Under such treatment the prognosis is fairly good.

It is gratifying to note that comparison of the value of the open and the closed methods of drainage in empyema is steadily yielding to consideration of the appropriate treatment for the individual or for the stage or type of the condition. Any careful study of a series of cases over a sufficiently long period of time will show that the mortality of empyema varies with that of pneumonia for the locality and the year although the method of treatment remains constant.[69] The principle which should be universally accepted is to avoid the creation of an open pneumothorax during the formative stage before stabilization of the mediastinum and later to use the type of drainage which is effective. The successive steps of such a course could consist of aspiration repeated as frequently as every four hours if necessary in the early stages to relieve symptoms of pressure or absorption, closed drainage by trocar-cannula-catheter method for twelve to eighteen days when the contents of the cavity are thicker, replacement of the catheter by a larger tube if necessary, and rib resection if drainage by these methods is not adequate. Such treatment is intelligent and rational and is based upon good surgical judgment of the individual requirements of the patient. It may result in recovery at any stage as shown by the fact that in over 400 cases rib resection was necessary in only 15. The fluoroscope is a valuable aid in determining the stabilization of the mediastinum.[70] When localization and stabilization have occurred, the fluoroscope will show no motion of the mediastinum or diaphragm of the affected side and increased motion of the opposite side. Under these conditions the empyema has become a walled-off abscess, pneumothorax can do no harm, and drainage is indicated. If the opening in the chest wall is smaller than that of the main bronchus, or if by any means the passage of air through the chest wall is impeded, the development of normal negative pressure is rapid.

During the period of stabilization the general condition of the child should receive the most careful attention; toxemia, malnutrition and dehydration should be combated by blood transfusion and other appropriate measures. Drainage methods should be altered as rapidly as the local condition warrants, and, if the discharge is thin or small in quantity for a week or more, drainage tubes may be removed entirely. Daily supervision, however, is necessary after early removal of drainage tubes to prevent retention of discharge and pocket formation. Hospitalization can be markedly reduced by careful individualization of treatment.

GENITOURINARY CONDITIONS

An excellent example of the difference between the surgery of children and that of adults is found in the urology of children.[71] Venereal and prostatic diseases with their complications, and malignancy with the exception of Wilm's tumor are rarely seen, and tuberculosis is not common, while congenital anomalies occupy a prominent place and the small size and delicacy of the parts require special care and instruments. Such conditions as congenital cystic kidney, hydronephrosis, congenital obstructions, stenosis of the meatus, epispadias, exstrophy of the bladder, and hypospadias require treatment early in life and are rarely met with in adults.

A series of 101 cases of hydronephrosis in children under the age of fourteen years is reported in which 25 were less than two years of age.[72] Hydronephrosis, if silent, may be revealed only during the course of a routine urologic examination and under such circumstances may remain undiscovered until adult life. In children there is no typical syndrome, the symptoms often being due to the causative factor such as stone or other obstruction, or to sequelae such as chronic or acute pyelonephritis which is more common in children because it often follows one of the acute infectious diseases. Marked enlargement of the abdomen may be one of the first signs, as in Wilm's tumor, with the distinction, however, that the mass is tense and fluctuant instead of solid. Excretory urography is a valuable diagnostic procedure but must be supplemented by retrograde pyelography if there is the least doubt. Persistent pyuria is almost invariably present. In early cases the prognosis is good, but most frequently the patient is seen so late that the kidney has been destroyed and nephrectomy is necessary. One reason for delayed diagnosis when the condition is due to stone is the fact that pain, nausea, and vomiting are almost invariably attributed to some intestinal condition, and frequent or urgent urination to enuresis. Significant indications are the location of the pain in the region of the kidney or upper abdomen, the tendency to dribbling, and the passage of blood or pus.[73] Multiple roentgenograms are advisable as the stone may change position or there may be several. If there is sand or the stone is small and the infection is mild, treatment by antiseptics, diuretics, and forcing of liquids may be adequate; otherwise the treatment is surgical and should be instituted as early as possible to prevent serious kidney damage.

Congenital obstructions occur at locations of normal physiologic constrictions and are more frequently found at the neck of the bladder than at the other positions.[74] In such cases the presence of residual urine is significant. Cystography is of greater value than excretory or retrograde pyelography, but cystoscopy should not be done until

the pyuria has been improved by appropriate measures. Transurethral surgery is most effective, using a child's or infant's size punch, but a second operation may be necessary in cases of obstruction by valves if the function and residual urine have not returned to normal by the end of ten days. The recovery from chronic sepsis and the restoration of a normal urinary condition are striking and most gratifying in these cases. There is another position of physiologic constriction where the ureter leaves the pelvis of the kidney, at which point obstruction may be caused by congenital hypertrophy of the circular muscle fibers of the ureter comparable to pyloric stenosis.[75] Ordinarily, however, obstruction at this point is due to an aberrant or anomalous artery crossing the ureter, abnormal position of the kidney, or to a high or oblique position of the opening from the pelvis into the ureter. Before infection has occurred, urinalysis may be quite negative and diagnosis possible only on careful urologic examination. When there are hydronephrosis and vascular obstruction, a vicious circle develops,[76] the greater the obstruction the greater the hydronephrosis and vice versa. Symptoms may appear early, one case reported being in an infant of fourteen months. The treatment is surgical, consisting of division of the aberrant vessel if only a small part of the kidney is involved, removal of constricting bands, reimplantation of the ureter, or nephrectomy if there is extensive kidney damage. The function of the opposite kidney should always be proved satisfactory before surgery is attempted.

Tuberculosis of the kidney is not uncommon in infants, children and adolescents.[77] In most instances it accompanies tuberculosis in other parts of the body and often is present for over a year before the diagnosis is made. Attention is usually directed to the condition by the symptoms of cystitis. The greater the bladder involvement the less the possibility of return of the urinary system to normal under any form of treatment.[78] Frequency, urgency, persistent or recurrent pyuria and hematuria, and nocturnal incontinence are all highly suggestive symptoms, and the passage of caseous thrombi may cause renal colic. Tubercle bacilli can be found in the urine in practically all cases, and cystoscopy is diagnostic after symptoms have persisted for some time. In septic cases prolongation of life may require the removal of the more involved of the two infected kidneys. A rare condition simulating tuberculosis is actinomycosis of the kidney.[79] As with tuberculosis there may be chronic discharging sinuses in other parts of the body and careful search should be made for the organism, including a study of the mouth flora in the presence of carious teeth. Association with hay or grasses is not necessary. The presence of the organisms in the urine may be due to the rupture of an abscess into some portion of the urinary system and does not necessarily indicate a kidney infection. Bladder symptoms and involvement are rare—a point of distinction from renal tuberculosis—and pyelography is of little value. When renal tuberculosis or tumor in a child is suspected and the symptoms are inconclusive, this condition should be considered.

Many articles continue to appear in medical literature regarding the hormone treatment of undescended testis, and opinion seems to be crystallizing regarding some of its aspects. It is fairly uniformly agreed that it should not be used long before puberty on account of inducing premature sexual development and that it is useless in the presence of mechanical obstruction to descent but that there is no

harm in giving this type of treatment a thorough trial for six months before resorting to surgery.[80] The dosage is usually 200 rat units three times a week, but it may be given daily if stronger stimulation is desired. The degree of benefit varies, some testes descending completely and permanently from an intraabdominal position, others only partly, and others retracting after treatment is discontinued. Hormone treatment may be used as an adjunct to surgery with occasional advantage.[81] Perhaps the most rational approach to the subject is through a preliminary examination of the urine for the pituitary gonadotropic hormone.[82] This hormone is not present in the urine of normal children; therefore its absence depends upon normal pituitary and gonadal function. If it is present in the urine of a cryptorchid, the interpretation would be that the pituitary gonadotropic function is active but that gonadal activity is insufficient and that the testis should descend in response to hormone treatment unless prevented by mechanical obstruction. If the hormone is absent from the urine of a cryptorchid, it may indicate failure of the pituitary gland to produce the hormone, in which case there will be other evidences of pituitary dyscrasia. In the absence of signs of such dyscrasia, failure to demonstrate the hormone would indicate normal pituitary, and gonadal function and descent should occur in response to hormone therapy unless there is mechanical obstruction. In unilateral cases such findings would indicate normal gonadal function in the normally placed testis and in bilateral cases in at least one of the hidden testes, and, if descent does not occur, surgery should reveal the obstruction. The presence or absence of the pituitary gonadotropic hormone in cryptorchid urine seems to depend upon several factors, and until one or more of them is definitely demonstrable the general conclusion will continue to be that hormone therapy should be tried before surgery because both the presence and absence may depend upon a factor which will respond.

It has generally been considered advisable to delay ureteral transplantation for exstrophy of the bladder until normal control of the bowel has developed. This, however, was not done in an instance of an infant four months of age in which the ureters were transplanted to the bowel eleven days apart with good healing and discharge from the hospital nine days after the second stage.[83] It will be of interest to note whether there will be later difficulty in establishing normal sphincteric control, and, if not, there should be no objection to shortening the period during which the child and the parents are objects of pity, curiosity, and sympathy.

Suggestions for simplification of the operative treatment of hypospadias are always welcome. In a series of nine cases, five of which have been completed and the remainder are in various stages, the repair proceeds in stages, advancing the opening of the urethra a short distance each time by a technic somewhat resembling the Ombrédanne.[84] No diversion of the urinary stream is necessary. The result in one case followed for more than four years is quite satisfactory, although sufficient time has not yet elapsed to determine whether the inclusion of a very small portion of hair-bearing skin will cause difficulty.

The treatment of hydrocele by injection of sclerosing substances which is so simple and popular for adults is not recommended for children because of the possibility of later development of hernia.[85]

In the series reported only two children were included—a rather limited number upon which to base conclusions even if both children developed hernia. In view of the excellent results which follow excision of hydroceles in children and the ease with which an associated hernia can be demonstrated and repaired, it would seem inadvisable to inject an irritant agent in close proximity to essential undeveloped structures unless surgery is definitely contraindicated.

ORTHOPEDICS

The term "faulty posture" as ordinarily used refers to an abnormal increase in the physiologic kyphotic and lordotic curves of the spine and calls to mind a series of charts showing varying degrees of round shoulders and protuberant abdomens. Such charts also show figures which are supposed to be the goal of corrective efforts. A study of the physiologic effects of the correction of such postural defects[86] brings out several facts which should be considered by all who are concerned in such correction. Faulty posture may occasionally be compensatory for another condition and should not be changed. The amount of correction should be individualized rather than designed to bring all children to a fixed standard which in some instances would amount to an overcorrection, the maintenance of which would require an effort out of proportion to the value obtained. Too rapid correction may be fatiguing and so reduce or counteract the benefit which might otherwise be obtained. Differences in results do not depend so much upon the degree of the defect as upon the degree to which the subject is handicapped by the defect, and for each individual there is an optimum posture to give the maximum therapeutic benefit. In some instances the effect of correction is spectacular—resulting in marked improvement in circulatory and respiratory efficiency. Other beneficial effects are to be noted in digestion, bowel function, and increased resistance to infection.

An interesting theory regarding certain congenital deformities attributes them to abnormal intrauterine pressure or to normal pressure exerted upon the fetus in an abnormal position.[87] Normal pressure on a normal fetus produces convexity of the back, while abnormal pressure increases this convexity and possibly causes local interference with nutrition and development, resulting in spina bifida. Pressure of the uterine wall is normally taken by the soles of the feet resulting in the usual calcaneous position, but with an abnormal position of the feet the pressure may produce any of the varieties of clubfoot. Immediately after birth it is easy to place the parts in the position in which they have developed, demonstrating how excessive pressure could have produced the deformity. Dimpling results from pressure on bony prominences such as elbows, knees, ankles, etc., and does not occur on points which are not exposed to pressure. Local ischemia is a possible cause of fibrosis of the sternomastoid muscle causing torticollis.

A study of congenital malformations which are not of mechanical origin indicates a strong hereditary factor.[88] In a large, carefully studied series defects appeared in siblings of malformed children twenty-four times as frequently as in the population at large. The identical defect was repeated in about 50 per cent of the cases. The identical malformation appeared in a distant relative in 41 per cent. The conclusion deduced is that most of the malformations studied

result from a defect in the germ plasm and exist before fertilization; hence, if there should be reason during pregnancy to suspect the presence of some congenital deformity, a study of the family history will give a reasonable indication as to its character. The study also gives an answer to the question often asked by a mother after the birth of a defective child as to the possibility of a repetition in subsequent children. Other studies have indicated that a deformity is more likely to repeat in a succeeding pregnancy which occurs after a rather short interval than in one which follows a long one. The study of heredity in the human animal is beset with many difficulties because of the paucity of offspring, ignorance of conditions affecting ancestors, inaccuracy of family records, prejudice, superstition, and many other factors; and advance can be made only by accurate, painstaking accumulation of a vast amount of data which can be analyzed in some such clearing house as The Eugenics Record Office.

An interesting and rather unusual condition affecting the thumb in children is similar to trigger finger.[89] It is a flexion contraction of the distal joint caused by a fusiform thickening of the tendon near the base of the thumb. Extension is halted at a definite point and then by continued effort is completed with a jerk, and in some instances cannot be completed. It is due to the fact that the thickened portion of the tendon is caught at an opening in the tendon sheath. It does not tend to improve, and surgery is necessary to enlarge the opening as physiotherapy and stretching are of no value.

Primary bone tumors occur rather frequently in children.[90] The benign forms are osteoma, osteochondroma, exostosis, chondroma, bone cysts, and sunray hemangioma. The last named is frequently confused with sarcoma but grows much more slowly and has a characteristic appearance in the roentgenogram.[91] In flat bones it produces a conspicuous projection showing well-defined radiating spicules, and in the long bones either a loose soap bubble appearance or the sunray picture. Biopsy may cause troublesome bleeding, and removal is contraindicated because of the danger of serious hemorrhage. If the diagnosis can be made before deposit of dense bone has occurred, roentgenotherapy is highly effective in stopping growth and pain. Other bone tumors are malignant or potentially so and require most careful study and care. Some are radiosensitive, the effect being temporary or permanent according to the type. Other types require amputation. Some are rapidly and others slowly malignant. Ewing's tumor—diffuse endothelial myeloma—is always confused with osteomyelitis and is so difficult to differentiate that Bloodgood's rule should be applied: If a destructive bone lesion is not positively known to be inflammatory, it should be considered malignant and be irradiated. When aspirated material is sterile, surgery is contraindicated because these tumors tend to metastasize early, are frequently fatal, and are extremely sensitive to irradiation.

The importance of proper care of anterior poliomyelitis during the early stages cannot be overemphasized.[92] It is most essential at first to keep the affected limbs in the "neutral position." This is a position of very slight flexion rather than straight, and is maintained by pillows, sandbags or plaster shells during the febrile stage. The back should be straight to avoid the tendency to scoliosis. Massage, exercise, and electricity of any kind at this time are absolutely contraindicated. After the temperature is normal, splints or casts maintain

position and allow relaxation and rest of paralyzed muscle groups, favoring recovery of tone and strength. At all times the patient should be protected from infections and the muscles from stretching. Gentle passive and active movements in a warm salt water pool are excellent and provide a mental stimulation which goes far in maintaining morale. Physiotherapy should be gradually increased and continued as long as there is improvement. The chronic or stationary stage presents problems requiring surgery and the use of apparatus.

Certain facts regarding spinal growth are of general interest and are essential for intelligent treatment of scoliosis.[93] There is no increase in the vertebral height of boys after the age of seventeen years, the average being sixteen years, and of girls after sixteen years, with an average of fourteen years. Spinal growth is slow in boys from the ages of four to eleven and in girls from three to nine and is rapid during adolescence. If there is scoliosis, it increases rapidly during the periods of rapid spinal growth and will not increase after growth ceases. Exercises to increase the flexibility of the spine do not tend to increase the curvature. The efficacy of any method of treatment must be judged during the period of rapid growth. It is of interest to note that, although a curve is held in a corrected position by mechanical means for some time after the end of the growth period, it may still be expected to increase somewhat after the support is removed and that even after spinal fusion an average increase of 14 degrees in the curve occurs in 23 per cent of the cases.[94] It would seem from this that hope of retention of improvement must be based upon development of muscle tone and power by consistent, persistent exercise until long after the end of the growth period.

Marked improvement in the healing of fractures which show a tendency to nonunion and in one case of fragilitas ossium is reported following the use of splenic extract,[95] the theory being that one of the functions of the spleen may have to do with calcium-phosphorus retention. In cases in which the more usual methods have not produced results, this treatment is worth a trial. Its use in this connection was suggested by the benefit observed following the use of splenic extract in osteomyelitis and tuberculosis of the bones and joints.

Congenital dislocation of the head of the radius, while rare, is to be borne in mind when dealing with elbow deformities.[96] The head of the radius is freely movable, is displaced forward, and will not remain when replaced in its normal position. There is no evidence of local swelling or trauma. At operation no orbicular ligament can be found; the head of the radius is outside of the joint capsule; there is no lesser coronoid fossa; the radius is longer than normal; and the head is misshapen. Roentgenograms show slight abnormality in the contour of the upper portion of the shaft of the ulna and in some instances a small area of ossification in the soft tissues overlying the head of the radius suggestive of the sesamoid type of ossification occasionally found over the head of a congenitally dislocated hip. No treatment is recommended unless there is definite interference with function, in which event removal of the head of the radius is preferable to attempted reduction, which may increase the disability. Correct diagnosis is important because the condition may be discovered during a roentgenologic study for some other condition, and the blame may be attached to the physician for failure to reduce the dislocation.

Fractures in the newborn are of interest alike to the obstetrician, pediatrician, surgeon, and orthopedist.[97] In a review of 115 cases the bones most frequently affected were found to be the clavicle and the humerus. In most instances fracture was not due to poor technic but to unusual obstetrical measures necessary to obtain a living child. Careful postnatal examination of every infant is advisable, for early treatment is essential, and one-third of these fractures were not recognized at the time of delivery. After five days it is usually impossible to obtain satisfactory manual reduction because of the rapidity of callus formation, and permanent deformity may result. During the first few days there is little muscle spasm, and accurate realignment is not difficult. In fractures of the clavicle good results may be obtained by holding the shoulders back with a skein of yarn; for the humerus, coaptation splints, an internal angular splint, or moulded plaster with an axillary pad and swathe give good results; and for the femur overhead skin traction on a Bradford frame may be used. Great ingenuity and care, with infinite attention to detail, are necessary in each case because of the delicacy of the skin, the tendency to pressure sores, and the difficulty of maintaining the position of fragments of a tiny bone enveloped in a large mass of soft contractile tissue.

Fractures at the neck of the femur are of great importance in children because serious disability in later life may follow failure to recognize and treat them properly.[98] Such fractures are the result of severe injuries and are often associated with other fractures which so claim the attention that the lesion in the hip may easily be overlooked. Symptoms of hip injury under such circumstances are always an indication for careful roentgenographic study. These fractures are of three kinds—epiphyseal separation, transcervical fracture, and cervicotrochanteric fracture—the last being most frequent. There is usually a slight shortening of the leg with prominence of the greater trochanter, abduction, and external rotation. In the ordinary fractures of childhood moderate deformity due to displacement of fragments is often overcome and corrected by the normal tendency for growth and repair, but this is not true with this type of fracture. Bony union takes place quickly and may result in malunion in a coxa vara position, the head uniting even as low as the lesser trochanter in some instances. This deformity tends to increase with weight bearing and may lead to extreme disability in later life. If seen before union has begun, continuous traction for eight weeks is advised with protection from full weight-bearing for an additional three months.

Acute osteomyelitis is always serious and often fatal, and the mortality is favored by blind adherence to routine treatment. In few conditions is recovery so dependent upon a careful evaluation of individual reactive ability, minimum disturbance of reparative processes, and nice adjustment and choice of supportive measures and agents. Even when every aid which clinical observation, surgical judgment, and laboratory data can supply has been carefully correlated and focused upon the case, too often a fatal outcome cannot be averted. The infection is usually hematogenous, and the picture is that of an acute general septicemia complicated by local infection in one or more places. It is often impossible to find the portal of entry, and in the great majority of cases there is no history of predisposing trauma.[99] Although early incision and drainage is indicated in many instances, it is unnecessary when it cannot remove the focus or all

of the foci or control the bacteremia.[100] The mortality in the early stages, regardless of treatment, is the same as that of an acute general bacterial infection. When the symptoms are predominantly those of a systemic infection, treatment should be directed primarily toward improvement of the general reactive ability and the local condition should be disregarded except when it seems probable that a definite focus is feeding the general infection. In an overwhelming general infection the local lesion is merely an incident, and operation does no good because the blood cultures usually remain positive and death occurs within a week. When operation is indicated, it should be well controlled and carefully planned with a minimum amount of trauma and disturbance of the localizing process. When the symptoms are essentially those of a localized infection with the general symptoms secondary, the blood culture may be negative and the reactive ability good. In such instances immediate drainage is advisable, but extensive surgery is contraindicated, the procedures being limited to adequate drainage, vaseline packing, and immobilization.[101] When the process is near a joint, sudden relief of pain may occur when it ruptures into the joint cavity thereby decompressing the bone. Definite involvement of an adjacent joint should be determined by aspiration before it is opened; joint symptoms may occasionally be due to the proximity of the process rather than to actual infection. Persistence of a positive blood culture indicates a bad prognosis, and the patient will usually die or show definite improvement within a week regardless of the type of treatment. Osteomyelitis due to staphylococcus infection is particularly serious, the patients showing positive blood cultures and marked toxemia frequently with disorientation. Staphylococcus antitoxin is of value in combating the toxemia, being used in daily doses of 32,000 to 160,000 units—the frequency and size of the doses being controlled by the Schilling hemogram.[102] The segment-nonsegment ratio is somewhat simpler than the complete hemogram and is of good prognostic value. A segmenter percentage as low as 15 to 25 indicates a serious weakening of the defense mechanism, and a return toward the normal of 60 per cent is a favorable sign. The antitoxin has no direct bactericidal effect, the blood culture often remaining positive for some time. It does, however, have a secondary antibacterial action by neutralizing the toxins which inhibit normal phagocytic activity. Neosalvarsan apparently has a definite bactericidal effect.[103] It is used in doses of 15 mg. increasing to 45 mg. administered every three days. Of thirteen patients receiving this treatment, three died, while of the seven not receiving it, six died. The series is small, but the results are so striking that the treatment is being continued in additional cases and gives promise of being a valuable contribution to the treatment of this serious condition.

After the stage of general septicemia has given place to that of localization, the problem of drainage and preservation of function assumes major proportions, and for this purpose the salt water pool treatment is excellent.[104] The Orr treatment provides adequate drainage and rest and in most cases gives the highest percentage of recovery that has been attained by any form of treatment. When, however, the process is close to one of the major joints, such as the knee, and is complicated by a suppurative arthritis, the problem of preservation of function is not best met by prolonged immobilization. In children it is especially important that motion of the affected joint should be

not only painless but that the fear of pain should be eliminated, and motion in the salt water is most effective in this respect. At first the bone is widely saucerized and packed with vaseline gauze, the infected joint is opened and irrigated, and the parts are immobilized in a cast for from four to six weeks. At this time the pool treatment is begun, fixation by splint being continued between treatments. In suppurative arthritis the joint is widely incised and irrigated with several gallons of warm normal saline, but the period of immobilization is only two or three days. In both types of cases the treatment is given for about thirty minutes daily. The temperature of the water is about 96 degrees, and the salt concentration is between 6 and 7 per cent. Weight-bearing can be easily regulated by varying the depth of the water. Motion in the water mechanically removes the products of infection and, because the water is hypertonic, osmosis promotes drainage from the innermost depths of the wounds. Under this treatment there is a distinct improvement in the period of disability and in end-results. In eight cases of arthritis involving the hip, knee, or ankle, the average healing time was three months, with complete restoration of motion in five months. If there is adjacent osteomyelitis, the period of treatment is longer, and there may be occasional ankylosis or limitation of motion. In cases of osteomyelitis without joint involvement there is a better range of motion and more rapid return of the surrounding muscles to normal than with the usual forms of treatment.

A careful study of tuberculosis of the hip in 90 cases followed over a period of many years under various forms of treatment strengthens the opinion that the best permanent results are obtained by fusion.[105] This should not be done until physical and roentgenographic examinations have definitely proved the process to be quiescent. By fusion the case is changed from one of joint tuberculosis to one of tuberculosis of a long bone; the disease has not been eradicated, and general measures for complete arrest must be continued for at least five years. It is essential that fusion be complete as a small amount of motion is useless and probably dangerous, attempts at restoring motion in cases which have been arrested for as long as four or five years having proved disappointing. Carefully controlled observations on the effect of heliotherapy in New England have indicated that it has no specific advantage over the other usual forms of antituberculosis treatment—a moderate amount of sunshine being of benefit to any person whether tuberculous or not. Secondary infection of a tuberculous abscess is to be avoided with the utmost care as it will heal spontaneously if the infection can be avoided. If secondary infection occurs, dependent drainage and immobilization are indicated. In cases in which the position necessary for dependent drainage is difficult, the abscess cavity may be filled with warm sterile vaseline after gentle thorough preparation and allowed to heal from the bottom as the vaseline is gradually forced out.[106] The skin must be protected by a thick coating of vaseline over a large surrounding area to avoid maceration by the discharge; the dressings are not changed for six weeks. The cast, as well as the dressings, becomes saturated with the secretions usually within a week, causing an offensive odor. Healing requires from three to twelve months under this form of treatment.

Symptoms strongly suggesting tuberculosis of the hip may be caused by a sterile synovitis of the hip joint,[107] the roentgenogram

and Mantoux test, however, are negative. The treatment is the same as the early treatment of tuberculosis of the hip from which the condition can be differentiated only by the fact that it disappears completely within two months.

The indications for the use of open or closed reduction of congenital dislocation of the hip are fairly definitely determined by the age of the patient. While a sharp line cannot be drawn, closed reduction is most successful in children under five years of age. The gentler methods of Denucé are preferable to the more vigorous ones formerly attributed to Lorenz. In cases of longer duration open reduction with retention by means of a shelf of bone or stabilization by the shelf procedure without reduction is indicated if closed reduction is not easily accomplished.[108] This condition should be kept in mind during examination of the newborn infants and all examinations of infants, for closed reduction at this period can often be effected without anesthesia by simple abduction with very slight manipulation and retention by plaster. At open operation the decision to replace the head in the acetabulum or to stabilize it in its acquired position will depend upon conditions found. If there is marked deformity of the head or acetabulum or if considerable force is necessary for reduction, there will be a distinct degree of limitation of motion, and the disability will be greater than if the head is allowed to remain outside the acetabulum. Open reduction is also indicated in younger children if closed reduction does not result in a stable hip after six months' retention in plaster. Prognosis should be reserved in all cases because, with physical development and increase of weight, conditions about the hip undergo structural changes, and a result which is good at the end of two or three years may become a bad one after the age of puberty.

TREATMENT

The determination of the sedimentation rate of the red blood cells is a procedure which is not as widely used as its value deserves. Taken in connection with the leucocyte count, it gives additional diagnostic information which may be of great assistance.[109, 110] The rate at which the red cells settle out of the serum is thought to be influenced by the presence of some substance which appears in the serum as a result of tissue destruction and by the relation of this destruction to reparative processes, the rate being rapid when destruction is greater than repair. Thus it is an index of the physical recovery from an inflammatory process, whereas the leucocytic reaction is an index of the state of resistance to bacterial toxins. The factors influencing the rate are not well enough understood to permit further generalization, but specific observations indicate that the rate is not increased in acute appendicitis before rupture or in subacute appendicitis, whereas it is increased in all other conditions which cause acute abdominal symptoms. It is high in osteomyelits and during the active progress of arthritis and tuberculosis of the bones and joints and returns to normal gradually with satisfactory healing. After every operation the rate increases, the increase beginning within twenty-four hours, accelerating for three or four days and gradually dropping to normal over a period of two to three weeks. In children with acute intestinal symptoms which are not considered typical of appendicitis, an increased rate speaks against appendicitis. In definite

appendicitis of over thirty hours' duration a normal rate together with a high leucocyte count indicates catarrhal appendicitis, while an increased rate with a high count indicates perforation. In all bone and joint conditions a normal rate should be present for some time before corrective surgical procedures are instituted or functional activity permitted.

The maintenance of a proper water balance is of particular importance in children because of their requirements for growth and development, a fact which is especially to be considered postoperatively. Water constitutes from 65 per cent to 70 per cent of the body weight. It is contained in the various vessels, ducts, reservoirs, the interstitial spaces, and the cells, between which there is a constant interchange. Surgical patients lose fluid by bleeding, vomiting, drainage and fistulas as well as by the kidneys, bowels, lungs, and skin. There is very little excretion of fluid by bowel, less than 200 c.c. per day unless there is diarrhea, the skin and lungs excrete from 800 c.c. to 1,500 c.c. per day under ordinary circumstances, and the kidneys excrete what remains after tissue requirements have been satisfied, an adequate output in children being 1,000 c.c. to 1,200 c.c. per day. The usual loss of fluid in the adult during the operative and postoperative period is about 1,000 c.c., thus giving a good idea of the care which should be exercised in children, the fluid requirements of whom are more exacting. Vaporization accounts for approximately 70 per cent of the loss which is increased by the perspiration encouraged by hot water bottles and increased bedding after operation. It is well to use the same amount of bed covering as preoperatively. Signs of serious dehydration develop when the loss of fluid approaches 6 per cent of body weight; in estimating an adequate supply this amount should be added at first to the amount necessary to meet the ordinary requirements.[111] The water content of ordinary solid food averages about 90 per cent, which includes the usual moisture and the water derived from oxidation. The choice of solutions to maintain an adequate postoperative water balance will depend on the circumstances. Saline is necessary if there has been loss of the gastric hydrochloric acid; glucose solutions supply a quickly available carbohydrate to replace depleted glycogen reserve and support liver function; and Ringer's or Hartmann's solution supplies electrolytes when there has been a long-continued loss of tissue fluids through fistulas or discharging wounds and an inadequate food intake. Glucose in distilled water is of value when food must be supplied in the presence of tissue edema due to chloride retention. By careful observation and estimation of fluid losses checked by blood chemistry, the requirements of the individual can be analyzed and an adequate water and salt balance can be maintained by intravenous therapy over long periods. Edema may result when the plasma protein of the blood falls below 5 per cent, which condition may occur if there is gradual loss of fluids through wound discharge or from burned areas or if the proper balance of diet has been disturbed by protracted illness.[112] Such edema is to be differentiated from that due to salt retention and is to be treated by blood transfusion. Sucrose solution is valuable for reducing intracranial pressure as it does not diffuse into the cerebrospinal fluid and cause a secondary increase of pressure. It is excreted unchanged by the kidneys and, because of its powerful diuretic effect, it is of value in reducing the edema of nephrosis or cardiac disease which is not

primarily due to a disturbed salt balance. It is used in 50 per cent solution given at the rate of 10 c.c. per minute up to 5 c.c. per kilogram of body weight. In treating acidosis sodium lactate solution—1.8 per cent—is preferable to sodium bicarbonate as the lactate is converted into glucose and is available for body requirements. It is an excellent supplement to saline solution in the treatment of acidosis but is contraindicated in alkalosis with dehydration, as in excessive vomiting. It is isotonic and may be used interstitially as well as intravenously. In marked dehydration with insufficient urinary output, it is well to start kidney function by 5 per cent glucose intravenously, adding solutions of the necessary salts later.

In shock from all causes except hemorrhage very little fluid actually leaves the body. The primary feature—low blood pressure—is due to increased capillary permeability and to vasodilation which permits loss of the circulating fluid into the tissues, and recovery depends upon restoration of the circulatory volume.[113] Whether the cause of the shock is trauma, toxemia, neurogenic disturbance, or drugs the picture of blood concentration is the same. In a study of shock caused by burns and freezing, the common practice of slow thawing was shown to be unnecessary, the tissue damage being dependent upon the freezing and not the speed of thawing.[114] In all types the decrease in blood volume results in a lowered alkali reserve and the production of acidosis, from which inhalation of carbogen gives temporary relief while the patient is being prepared for blood transfusion. The acidosis causes a fixation of fluid in the tissue cells interfering with its return to the blood vessels. Improvement due to the use of hypertonic solutions is transitory, and the treatment of choice is blood transfusion. A study suggested by the picture of blood concentration has been directed toward methods of obtaining and preserving normal serum, the theory being that except in anemia the proportion of blood cells is above normal, and the deficiency is in the plasma.[115] An interesting observation is that there is no danger of agglutination of the cells of the recipient by the serum of the donor and hence serum from all blood groups can be used. The great advantage is that, whereas blood can be stored for only about thirty days, serum may be preserved for long periods. A method of separating the cellular elements from the plasma without trauma is being investigated.

Blood transfusion is often an emergency measure, and its use under such circumstances without preliminary testing is entirely justifiable. Whenever possible, however, determination of compatibility should be carefully carried out.[116] Grouping and cross-typing should both be done as there are occasionally subgroups within a group. In cross-typing it is not well to mix whole blood of the donor and recipient, but the recipient's serum should always be matched with the donor's cells. If possible, the donors should be relatives and of the same group rather than universal donors; there should be no history of syphilis, malaria, allergy, or communicable disease; the age of choice is between twenty and thirty years; the hemoglobin should be not less than 80 per cent; and blood should be taken a sufficient length of time after a meal to avoid reaction from products of digestion. It is preferable that a donor be used only once, and, if this is not possible, cross-matching should be repeated before each transfusion for, although normally the blood grouping does not change, the recipient

may have become sensitized or slight alterations in reaction may be produced by drugs, anesthesia, roentgenotherapy, and toxemia.[117] Death has occurred when this precaution was not observed.[118] Before transfusions of infants with maternal blood, cross-matching should be carried out, as the infant's and mother's bloods are not always compatible. Also a careful investigation as to intracranial hemorrhage should be made, and no elective operation or transfusion should be done before sufficient time has elapsed for an intracranial clot to become securely organized—a case of death having been reported during transfusion of an eight-day infant.[119] Death was caused by changes in blood pressure due to oozing from a circumcision followed by a transfusion of only 54 c.c. Reactions may be either proteolytic due to anaphylaxis or hemolytic due to faulty grouping. Untoward symptoms which may occur early in the course of the transfusion are a short, sharp cough followed closely by loss of consciousness, stertorous respiration, chill or convulsion, and rising temperature. Late reactions include shivering, headache, pain in the back, dizziness, nausea, vomiting, and at times urticaria. An interesting development is the continuous or drip blood transfusion,[120] averaging in adults a total of five pints given over a period of twenty-nine hours. It is indicated in anemic states, but it is not to be used when the hemoglobin is normal. It is also excellent treatment for exsanguination and collapse. For children the total amount is somewhat less than for adults, but the transfusion is continued until there has been a satisfactory increase in hemoglobin. The rate in small children may be as slow as five drops per minute and may be gauged so that the rate of increase in hemoglobin is not over 10 per cent every four hours. The total normal blood volume of a child is considered to be $\frac{1}{11}$ of normal body weight, and the administration of $\frac{1}{10}$ of this calculated volume in nonbleeding cases should produce a rise of 10 per cent in the hemoglobin. It is often necessary to use four or more donors for a single transfusion all of whom must be of the same group. The blood is citrated and during the transfusion oxygen is bubbled through it to prevent sedimentation and concentration of the red cells. Improvements in the apparatus are being perfected.

A new substance for the treatment of hemophilia is being investigated.[121] It was accidentally discovered that, if egg white is incubated for several days at 37° C. in the presence of potassium bromide, a substance can be extracted which may be used intravenously or intramuscularly with marked improvement in the bleeding and coagulation time. In specific instances the clotting time has been reduced from ninety minutes to one and two-thirds minutes, from thirty-five to six minutes, and from one hundred and ten minutes to seven minutes. Repeated injections are necessary, and improvement is gauged by the therapeutic test. Until further reports are available, however, ovarian extract and snake venom[122] will continue to be the treatment of choice. The venom acts by temporarily decreasing the permeability of the capillary wall. The duration of treatment is from one week to four months, and the period of freedom from hemorrhage has been observed to be from one to twelve months.

INFECTIONS

The serious consequences of infection and thrombosis of the cavernous sinus by transmission of material from infected lesions of the face by way of the angular veins is well recognized. Ligation of this vein

is not difficult but is usually resorted to only when absolutely necessary on account of the desire to avoid incisions in healthy tissues in the presence of adjacent spreading infection. To avoid this, temporary occlusion of the angular and infraorbital veins was produced in one case by an apparatus which exerted pressure through a sponge rubber pad.[123] The apparatus remained constantly in place until developing resistance overcame the infection. In younger children difficulty can be foreseen in obtaining cooperation, but with older children the method would appear to possess possibilities.

Rapid improvement is reported following roentgenotherapy in cases of erysipelas, lymphangitis, infected hemangiomas, and parotitis which on rare occasions follows abdominal surgery.[124] The infection is frequently controlled in two to three days, drainage may be avoided, and, if drainage has already been established, discharge is markedly improved. This report is of interest in connection with the roentgenotherapy of mastoid infection noted elsewhere in this review.

As a local application for infected wounds, compresses of equal parts glycerin and alcohol are recommended[125]—the principle involved being dehydration of the tissues with the secondary advantage of prevention of additional infection. The solution and dressings should be changed at intervals of not more than eight hours, preferably every three hours, as hygroscopic action draws fluid from the tissues diluting the solution. Products of infection and bacteria are carried away, and bogginess of the tissues is reduced permitting an improved blood supply and access of antibodies. Massage or compression of tissues is carefully to be avoided in changing dressings. The proportion of alcohol may be reduced if the temporary stinging is a cause of too great discomfort in children. When this type of dressing is applied before localization, absorption may occur.

Successful treatment of staphylococcus infections showing positive blood cultures depends upon the development of his own antibacterial substances by the patient.[126] This organism produces an exotoxin as well as an endotoxin, the former causing hemolysis, killing the leucocytes, and tending to coagulate plasma. If this toxin can be neutralized, time is gained for the development of antibodies. This is best done by staphylococcus antitoxin. Transfusions of blood are valuable also for three reasons: to replace destroyed red cells, to obtain the effect of whatever natural antitoxin may be present in the donor's blood, and to add fresh human complement. Immunotransfusion is of assistance in chronic cases, but the production of specific immunity in a donor requires too much time to make it practical in severe acute infections. In these the use of nonspecific immunotransfusion may give good results. The antibacterial value of neosalvarsan has been noted under the treatment of osteomyelitis earlier in this review.

Wounds caused by explosions or contaminated by clothing or soil may be infected with anaerobic organisms.[127] The diagnosis is usually evident within forty-eight hours but previous to that time may be determined by placing a bit of the necrotic or macerated tissue in an agar stab culture and covering the stab with melted agar. If gas infection is present, the agar will be blown out after incubation for about four hours. The roentgenogram will show gas bubbles in the soft tissues earlier than they can be palpated, and roentgenotherapy is often valuable. Pain is out of proportion to the amount of injury,

there is local pallor and swelling with increased pulse and temperature, flushed face, and clear intellect. In about twenty-four hours there may be a dirty, creamy, serous discharge, and a greenish gray membrane forms which gives off a characteristic musty odor. Early cauterization of such wounds is contraindicated because the necrotic tissue resulting is an excellent culture medium for anaerobic organisms. Free incision, débridement, and potassium permanganate, or hydrogen peroxide packs are indicated, and general support by blood transfusions and serums is of value. Amputation may be necessary.

Zinc peroxide is being most favorably reported in the treatment of wounds infected with anaerobic, micro-aerophilic, and certain aerobic bacteria, including hemolytic streptococci, gas bacilli, and tetanus bacilli.[128] The diagnosis should always be made by bacteriologic identification. It has been used with success in a great variety of infections among which are lung abscess, chronic empyema, fecal fistula and fistula of the abdominal wall, gangrenous skin infections, gunshot and street injuries, human bites, and infections of the face, neck and mouth. It may also be used in preparation for tonsillectomy or plastic surgery of the mouth, especially if the presence of Vincent's organisms is shown or suspected. A small amount may be swallowed without bad effect. Before application to an infected area the necrotic tissue and overhanging edges should be removed as thoroughly as possible because it is essential that the substance come in actual contact with the organisms. It may be applied on gauze, injected to the bottoms of the sinuses, or sprayed; it must reach all recesses. After application of saturated gauze the entire area is sealed with vaseline gauze. The dressings should be changed daily except that, if the wound is painful, they may be allowed to remain for two days at first. When the dressing is changed, the old peroxide should be removed with water or saline. The improvement is prompt and marked both as regards comfort and reduction of infection; exudate decreases; granulations become red and firm; sinuses shorten; and undermined areas begin to seal down. The progress of treatment is checked by cultures, and, when the granulating area is clean, Reverdin grafts may be used to hasten epithelialization. The grafts may be held in place by a single layer of gauze sealed to the skin and covered with saline gauze for twenty-four hours, after which the saline gauze is replaced by the zinc peroxide dressing and in another twenty-four hours the innermost layer of gauze may be removed. Some commercial forms of zinc peroxide are inert. A suitable test is as follows: The substance, which is a fine white powder, is stirred into distilled water forming a thin suspension and is placed in a large test tube. If active, the powder settles quickly leaving a clear supernatant fluid in about thirty minutes. Small bubbles of oxygen appear in the sediment within an hour and by twenty-four hours the sediment is thoroughly raised by the gas. Before use the powder should be sterilized and mixed in distilled water with a syringe to a thick creamy consistency.

MISCELLANEOUS CONDITIONS

The presence of a thickened labial frenum is often a cause of much concern to mothers and has been the subject of a considerable amount of discussion among dentists. The sentiment among orthodontists, however, is gradually becoming more prevalent that the abnormal frenum

has little or no relation to the separation of the permanent central incisor teeth and that the scar resulting from its removal may interfere more with orthodontia which may later be necessary than would the frenum.[129] In some instances the abnormal thickening will disappear with the growth of the lip and superior maxilla, in others the permanent central incisors will erupt in good position even though the deciduous incisors are widely separated. If resection of the frenum should seem advisable, special attention should be paid to hemostasis, complete removal of the interdental portion, and careful closure of the mucous membrane to minimize scarring.

Cervical gland tuberculosis is steadily becoming a clinical rarity in those areas where there is close supervision of dairy herds with adequate legislation to control the tuberculous animals and where, in addition, there is practically universal use of pasteurized and certified milk. It occasionally is seen, however, and it is well to bear in mind the value of conservative treatment.[130] Incision is to be used only in case of definite pointing of an abscess, and then only if careful aspiration under the strictest aseptic precautions has failed to relieve tension. Excision is usually followed by recurrence and a rather marked degree of permanent scarring. Antituberculosis treatment should be prolonged over a period of years if necessary but will in the great majority of instances give results much superior to those obtainable by surgery.

Sarcomas of infancy usually occur in internal organs such as the kidney and are progressively fatal. That the outcome might be different if diagnosis could be made early is suggested by a case in which a subcutaneous fibrosarcoma was present between the scapulae at birth.[131] The tumor, which was 2 inches in diameter, was removed at the age of two and one-half months but recurred and was removed again at the age of six months. At that time infiltration of the surrounding tissues was so extensive that complete removal was impossible. Alternate growth and recession followed for eighteen months with no treatment whatever, when the mass finally disappeared and has not reappeared for seven years. There was, no doubt, infection, and the possibility of bacterial action similar to that of Coley's toxins seems probable. The reviewer has removed an extremely cellular fibrosarcoma of approximately the same size from the subcutaneous tissues of the flank of a four-week-old infant. This tumor was present also at birth when the overlying skin was apparently traumatized, making infiltration seem probable. Careful pathologic study, however, failed to demonstrate involvement of the surrounding tissues, and there has been no evidence of recurrence over a period of eight months.

Mastoiditis in infants and young children may cause symptoms much more suggestive of gastroenteritis than of mastoiditis.[132] There may be diarrhea, vomiting, dehydration, fever, and acidosis with great toxicity and prostration out of all proportion to the gastrointestinal and local signs. Mastoid infection takes place more easily in infants than in older children and adults because the eustachian tube is relatively shorter and larger, favoring infection by regurgitation; furthermore the inner ear is full of mesodermal embryonic material preventing drainage and encouraging absorption. There may be a defective suture line permitting direct communication between the cranial and tympanic cavities accounting for the early appearance of meningeal

symptoms. Interpretation of roentgenograms requires a thorough knowledge of the normal, as the mastoid process is absent at birth and does not approach the adult appearance before the third year. In cases which are definitely surgical, operation should not be delayed, but the intelligent employment of roentgenotherapy as an adjunct to surgery changed the basic indications for surgery in a reported series of 20 cases. Of these only three required surgery, two died, and fifteen recovered. It was considered that roentgenotherapy caused shrinkage of the embryonal tissues allowing freer drainage and also perhaps reduced the adenoid tissue which may have been blocking the inner end of the eustachian tubes and may possibly have had a direct effect upon the bacterial infection. One to three treatments are required, and they should be repeated if improvement ceases. It should be noted that this method of treatment is not offered as a substitute for surgical drainage but may be used while the infant is under close supervision so that the usual surgical indications are not overlooked. If there is an advanced state of malnutrition, an extension of infection into the mastoid may be indicated by an exacerbation of the diarrhea and increase in the temperature which is not otherwise explainable.[133] Such infants are poor surgical risks but may be improved by repeated small transfusions so that drainage with a minimum of surgical trauma gives an opportunity for recovery which rarely occurs otherwise. Purulent otitis media is sometimes complicated by suppurative parotitis.[134] The onset is sudden with fever, severe pain, and swelling of the parotid. Edema may be sufficient to close the eye and to cause motion of the jaw to be painful. Relief is usually prompt after incision of the parotid fascia anterior to the ear, but the course of the infection may be long and tedious.

Since brain tumor is not a rare condition in children, suggestive symptoms should be recognized early so that a thorough neurologic examination can be made or the child can be referred to a neurologic surgeon before the period in which successful treatment is possible has passed. These symptoms consist of vomiting usually of the projectile type and often unaccompanied by nausea, persistent or recurrent headache, particularly in the early morning, disturbances of vision or other special sense, awkwardness in the use of the hands, staggering gait, and changed disposition.[135] If the usual neurologic findings are not definitely conclusive, there should be no hesitation in the use of encephalography, as it often gives the final evidence necessary to confirm the diagnosis. The feeling of hopelessness and despair which the knowledge of the presence of an intracranial lesion engenders in parents requires the most positive diagnosis possible, even though the prognosis be bad, in preference to the false hopes raised by an incomplete or inconclusive examination.[136] The definite contraindication to encephalography is increased intracranial pressure due to a tumor in the posterior fossa.[137] If this condition seems probable, rest in bed and dehydration by fluid restriction and rectal administration of magnesium sulphate solution will usually give relief; if visualization of the cerebroventricular system is still considered necessary, it may be more safely accomplished by means of the direct ventricular approach. The conditions most suitable for encephalography and in which it is of greatest diagnostic value are atresia or maldevelopment of the brain, intracranial lesions from birth trauma or prenatal hemorrhage, inflammatory lesions, epilepsy, and brain

tumor, with the exception mentioned. It is best done under anesthesia, avertin being particularly good for this purpose, preceded by a mild sedative in an unusually nervous child. Complete drainage of the cerebrospinal fluid may be done if the fluid is removed in small amounts and replaced each time with air, requiring in some instances nearly one hour. If there is marked circulatory disturbance, it is advisable to interrupt the procedure temporarily or to discontinue it entirely. For the following few days there may be headache, drowsiness, vomiting, fever, and dizziness upon sudden movements of the head. These conditions disappear under the influence of rest in bed, and leave no after-effects. Encephalography is applicable in suitable cases to all ages from infancy through childhood.

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SEVENTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

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Round Table Discussion on Speech Defects

Chairman: Smiley Blanton, M.D., New York, N. Y.
Assistants: Earl C. Chesher, M.D., New York, N. Y.
Letitia Raubicheck, Ph.D., New York, N. Y.

Speech Disorders

Smiley Blanton, M.D.

Children are brought to the pediatrician because they do not talk, because their speech is imperfect and indistinct, or because they hesitate or are blocked in their speech, that is, they stutter. Perhaps it will be helpful to discuss speech disorders under these three heads: delayed speech, imperfect or indistinct speech, and stuttering.

The average child begins to use intelligible speech at about fifteen months. At two years he has several score of words at least. Occasionally, however, we find children who are two or two and one-half years old before they begin to talk. If, however, a child does not use words intelligently by the time he is three years of age, I think we are justified in assuming that something is very definitely wrong.

It is my experience that the most common cause of delayed speech is mental retardation. It is, however, very difficult to tell whether a child appears mentally retarded because he does not speak, or whether the mental retardation causes the delay in speech development. The average doctor's office is not equipped to test a child's attention, interest, and mental ability. Since play materials are usually lacking, we are often justified, I think, in withholding our judgment even though a child does appear mentally defective at a first examination. Such children should be observed at play, if possible in a nursery school environment where the observer can remain unseen. There are certain signs in the child which point very definitely toward mental retardation: first, a lack of interest in blocks, colored pictures, balls, dolls, and in such objects of daily use as a hairbrush, comb, shoes, or a piece of soap; second, attention which is very flighty or, on the other hand, fixation of the attention for too long on one thing; third, lack of effort to use play material in any constructive way; and, fourth, a lack of effort to dress himself or to feed himself. If these symptoms are present, we can be quite sure that we are dealing with a child who is mentally retarded.

In my experience most of the mental retardation that I see can be diagnosed as primary amentia. It is true that there are a good many children who have hemor-

rhages at birth or who have physical defects, such as physical and functional defects of their digestive or circulatory systems, but it must be remembered that the retarded child is defective physically through heredity and the physical defects that we see may be caused by poor genes. The physical defects are a sign of his retardation and not a cause of it. I have rarely seen a child who as late as four or five years appeared mentally defective, had no physical defect to account for it, and who subsequently turned out to be completely normal.

A type of speech rather difficult to understand occurs in children who have only a slight mental retardation and yet do not develop speech until very late. Frequently we see children with an intelligence quotient of 75, which is quite sufficient for the development of speech, and yet at the age of ten years they are not speaking. Perhaps we must assume in such cases that there is a specialized defect in the cortex of the brain concerned with speech.

The second most common cause for delayed speech is defective hearing. It is common knowledge, of course, that a child who is deaf will not learn to speak unless he is given special training by teachers who are specially equipped for this purpose, but we have found that children with even slight defects in hearing do not develop speech at the usual time. And there is another type of hearing defect which is a common cause of delayed speech: range deafness. This, as you all know, is a defect of hearing for certain tone ranges from the beginning of speech sounds which are about 75 vibrations per second to something like 6,000 or 8,000, which is apparently the top range for speech sounds.

It is of course very difficult to test hearing defects in young children. But by observing the child's response to sounds when he is not looking, one can determine to a certain extent whether the child has any defect of hearing.

Defects in sight, too, seem to have some influence on the development of speech. I have seen several children with defective vision who did not develop speech at the usual time. Apparently reading the lips is helpful to the child in developing the proper speech sounds. Another less frequent but somewhat important type of difficulty that causes delayed speech is prolonged illness. One such case is that of a child three years old who did not talk at all and who seemed so flighty and overactive that he *seemed* to be mentally defective. He had a history of having had pneumonia at the age of fifteen months, followed by empyema which kept him practically bedridden for six months. Following this he had a mastoid operation and some months later a second mastoid operation on the other ear. These illnesses lasted until he was about three years of age. This child was placed in a summer camp where he was given some speech training and the chance to build up his physique by exercise, to learn to develop his large muscles. In one summer he developed quite a sizable vocabulary.

Children who are not allowed to use their muscles in walking are very often slow in developing speech and sometimes actually seem mentally defective. An example of this was a normal child whom we saw during the War. The mother was stationed at an army post. Thinking that she was going to be moved at any time, she packed up all the furniture, including the rugs, so that the floor was bare and the child was kept on the bed. The winter passed without orders and when we saw the child in June, 1918, she was twenty-six months old, with no vocabulary whatever. When the child was given a chance to run and play freely and to exercise her muscles, she began to speak; in the course of the summer she developed an almost normal vocabulary. It is not uncommon at the present time to find children whose activity is so restricted because of slippery floors and because of stiff-soled shoes so that they are afraid to run and walk, and their vocabulary is quite limited.

In some cases, however, there seems to be a very definite emotional fixation which prevents a child from developing speech at the usual time. A case like this was a boy of three and a half years of age, normal physically, mentally alert, obviously

with superior intelligence, who did not have a single word. When he wanted anything, he either cried or pointed for it. There was an older brother eight years old, and there was a sister who died just before he was born. The mother very much wanted a girl. When this boy came, she, unconsciously of course, made every effort she could to make him into a girl. She waited on him and cared for him at the age of three years very much as if he were a child of six months. The mother was persuaded to send the child away to his aunt who had a child about his age, for three months, then he was placed in a nursery school for a year, and the mother was persuaded to change her attitude. In about a year he had a vocabulary of 20 words or so, but his speech was very defective. At the age of five he could talk freely but very indistinctly. At the present time he is eight years old. His speech is practically perfect, and his vocabulary is quite normal.

In some cases we must keep in mind that the child is not talked to enough. We saw a very unusual case once of a child of three years of age who had practically no speech whatsoever. The mother was evidently psychopathic. She saw the child only about one-half hour a day and did not talk to her very much, and she gave the nurse definite orders that she should not talk to the child. As a result, this little girl of three years had practically no speech whatsoever. By placing her in a different environment where she could receive normal attention and affection, she developed a vocabulary in a short time. Families vary a great deal in the amount of speech that is used. Children who are talked to a great deal usually have a very much larger vocabulary than those who are not talked to so much.

Stuttering, under which we include stammering, is probably one of the most interesting and difficult of the speech disorders that we have to deal with. Perhaps we can best understand stuttering by understanding the reasons for speech. As we see it, the child talks first in order to express his feelings. Speech then, as we see it, is the chief means by which the child gives vent to his emotions. And since he can do it so much better by words than he can by crying and yelling, the normal child finds it to his advantage to learn to talk. A second reason why the child talks is that it enables him to make an adjustment on a more adult level to the group. Speech, aside from walking, is the most important step the child makes toward an adult adjustment. As long as he cannot walk, as long as he cannot talk, he remains in an infantile dependent stage.

An analysis of the child's erotic life helps us to understand how stuttering develops. Suckling is the earliest and most primitive of the child's erotic pleasures. A little later the eliminative functions constitute an important factor in the child's erotic life. If there be a fixation of the child's feelings at the nursing level or the eliminative level, a certain amount of anxiety arises. This is caused by the fact that the child is scolded or at least meets with disapprobation when he tries to continue his nursing tendencies and his interest in his eliminative functions beyond the period of eighteen months to two years.

Again it must be remembered that speech makes use of the primitive muscular mechanisms involved in suckling, swallowing, vomiting, sneezing, and breathing. The speech area uses these primitive muscular organisms for the purpose of speech.

There is one other point that should be emphasized. Before the child learns to talk he has a great many sounds which are not suitable for English speech. Phoneticians tell us there are about 600 speech sounds in all of the languages, but English makes use of only about fifty-odd sounds. The child in learning to talk must repress the primitive gargling, suckling, vomiting, clucking sounds which he uses in the babble period. Stuttering, as we see it, is a lack of repression of the primitive speech sounds which the child makes in the babble period. If the child has too strong a fixation on the suckling or eliminative levels, there will be a tendency for the primitive sounds to break through into the patterns of speech. As a result, the child may have a stuttering symptom, which consists of a chewing movement, or

a complete blocking, which is a vomiting, eliminative movement, a suckling movement, a sneezing movement, an inspiratory or an expiratory breathing movement, and so on. All of the symptoms shown in stuttering may be referred to these primitive muscular movements which we have enumerated.

Along with this tendency for the child to regress back to these primitive movements there occurs a certain amount of anxiety. This is due to the fact that the child feels that this is something that meets with disapproval, that may lose him the love of his parents. This is the only explanation, we believe, that can explain why stuttering starts so often when the child begins to speak at the age of eighteen months. Perhaps an analogy may be helpful. An infant who is unsatisfied with his suckling periods sticks his thumb in his mouth and continues to suckle. Stuttering as we see it is similar to this. It is a continuation of the primitive speech sounds, which should be eliminated when the child begins to speak.

It is our belief that the nursing period of the child therefore is the time when proper hygiene both mental and physical can be invoked to avoid the development of stuttering. Children who have difficulty in nursing, who have digestive disturbances, who have bowel disturbances, are prone, we think, to develop neurotic reactions which may give rise to stuttering. From a practical standpoint we should say that an overuse of suppositories or an anxiety on the part of the parents as regards the child's eating and eliminative functions may very definitely lead, in the case of sensitive children, to the development of stuttering.

We do not wish to minimize the influence of the constitutional factors in stuttering. Undoubtedly in every case there are certain tendencies in the child which make it more susceptible to the development of stuttering. But since we cannot change the constitutional make-up of the child, the best we can do is to modify the mental and physical environment of the child so as to avoid the stresses and fixations which give rise to stuttering.

Of course, the symptom of stuttering does give rise to anxieties, to difficulties in themselves. We are emphasizing here the primary causes of stuttering and what may be done to avoid this early stuttering.

Language Problems in Children

(A Brief Statement of the Viewpoint of Dr. Samuel T. Orton)

Earl C. Chesher, M.D.

Dr. Samuel T. Orton found a close parallelism between the acquired defects in language due to brain injury and certain defects in language development. This parallelism suggested to him that he was dealing with a disturbance of the same physiologic mechanism in both instances. Since, in the adult, such a loss occurred only when the lesion was in the master hemisphere, his attention was directed to those factors which tend to determine the establishment of unilateral brain control. In his study of several hundred cases of children with language disabilities, he found a high incidence of mixtures of right and left motor preferences in the patients and a high incidence of language defects and both right- and left-handed forebears in the family background. Because of these findings, he suggested that a comparable intergrading exists between the critical areas of the various fractions of language faculty in the two hemispheres of the brain, and that this gives rise to a series of developmental defects in language.

Dr. Orton rejected the suggestion that these language defects are due to faulty development of particular brain areas because of (1) the high incidence of disabilities in the population and (2) the fact that the disability can be overcome with proper training.

Five language disabilities were recognized: *strephosymbolia* was used to describe the first. It is a symptomatic, descriptive term, which means twisted symbols. It

was used to characterize those who were unable to learn to recognize words at sight as did facile writers. Dr. Orton emphasized the point that inability to learn to read is not to be regarded as a specific defect unless it is distinctly out of harmony with the child's skill in other fields—notably the ability to learn by hearing and to master arithmetic concepts. To be classified as a specific reading disability, the defect must occur in the absence of visual, auditory, or general intellectual defect, and in the absence of any primary emotional defect, such as general apathy toward all school work or lack of adequate disciplinary home training.

The specific character of the disability is readily shown by means of an "educational profile" on which are recorded the grade, C. A., M. A., and accomplishment on standard tests of arithmetic, reading, spelling, and writing.

The group showing a specific reading disability was found to fall into two classes:

1. Those cases seen early before the influence of training has occurred.
2. Those cases who have acquired reading, but to so poor an advantage that failure in secondary school and college can definitely be referred to as residual confusion.

Four types of mistakes were commonly made by these children in their attempts to read the printed word:

1. Confusion in: b,d—p,q—b,d,h—m,n,u—a,s.
2. Confusion of reversible words: saw, was—dog, god—on, no.
3. Twisting of letters within a word: from, form—calm, clam.
4. Twisting of syllables: tarnish as tar-shin or rat-nish.

Dr. Orton speaks of this tendency to confuse the sequence of letters and syllables as the reversal tendency. He emphasizes its high incidence. He does not believe that this difficulty is due to any inability to see the word. He cites as evidence the fact that they make attempts to read the word even though these efforts did not bring correct recognition; and the fact that they could copy correctly words which they could not read. For these reasons, he felt that the difficulty is in recalling previous exposures of the word rather than in seeing the word.

These children who are unable to learn to read have also great difficulty in spelling. This is due to the fact that the word-picture, which is not sufficiently exact to serve as a basis for its recognition when the word is seen, is even less serviceable for the reproductive purposes of spelling. The distortions in the order of recall of letters in a word were quite similar to the distortions in reading attempts.

The fact that a large number of the children with reading disability showed mixed or crossed motor patterns was considered suggestive evidence that, as a group, they belong among the motor intergrades. This view is also supported by the finding that the family background, in the majority of the cases, revealed a high incidence of left-handedness and of language disorders of one sort or another.

The second language disorder described is that of *word deafness.* In these cases the primary difficulty is in the recognition of the spoken word, and there is a consequent delay and distortion of speech. These defects are seen although there is normal hearing throughout the whole of the audible range. These children are described as being able to hear the word accurately but unable to understand it. They understood and reacted correctly to all sounds of the environment except speech.

These children understand, to some degree, speech which is delivered slowly and deliberately and with careful enunciation. Often, a simple command is correctly understood whereas a series of such simple commands leads only to confusion. Marked auditory inattention is an outstanding feature.

The verbal output of the group showed many errors of both pronunciation and grammar. They were most likely to omit some of the sounds of the word, for example, "mind" for "remind"; or to distort the word—"astinctly" for "distinctly."

Dr. Orton makes the point that the entity regional deafness—a condition in which there is a reduced acuity in one region of the audible range—is frequently misdiagnosed as word deafness. The true nature of the disability can be ascertained only after a careful testing with an audiometer.

The third language disability considered is that of *motor speech delay*. In these cases, speech develops slowly, and usually with a marked defect in enunciation. It is easy to attract the attention of these children by speaking to them, and they listen carefully to what is said. They are likely to point to things they want rather than to attempt asking for them. Their spontaneous speech reveals a defective articulation. Dr. Orton states that the prognosis for this group is, if training is started early, better than for any of the other groups. Once speech is started, its development is likely to be rapid, although there may remain a slight defect such as a lisp, a defective "r," or some other infantilism, or a more severe defect such as stuttering. This group is especially late in establishing a preference for one hand or the other and testing shows most of them to be motor intergrades.

The fourth and fifth groups are labeled agraphia and apraxia. *Agraphia* is used for those who show difficulty in learning to write but show aptitude in the other aspects of language, which is in keeping with their general intelligence and training. This difficulty presents itself in two forms: (1) in which the writing pattern is an acceptable one, but the rate of performance is extremely slow; and (2) in which the rate of performance is normal, but the pattern is so poor as to be illegible.

The fifth group is that of *apraxia* or abnormal clumsiness. These children show a lack of skill on both sides which might be compared to the unskillfulness of the left hand of a strongly right-handed individual. They have great difficulty in acquiring skill in fine movements of the fingers and hands and may have difficulty in acquiring any complex trained movements, whether of hand, foot, or body.

Summary.—It is Dr. Orton's thought that the disabilities described spring from a common origin and are the result of admixtures of right- and left-sided tendencies. He emphasizes that motor intergrading is not to be considered a fixed measure of one's ability to acquire manual or linguistic skills. He looks upon it as evidence that the hereditary tendency to one side or the other is not sufficiently strong to establish a clear-cut selective preference for one side in all acts. He further stresses the point that it is those in whom there is some tendency toward left-sidedness, but in whom this tendency is not sufficiently strong to assure complete superiority of the right hemisphere, who form a fertile soil for the disturbing effects of misguided training.

An Outline of a Rehabilitation Program for the Speech Handicapped

Letitia Raubicheck

The essentials for any effective reeducational program are early discovery, accurate diagnosis, and a planned program under expert guidance, persisted in until correction or at least an optimum condition has been reached. This paper will endeavor to outline the way in which the Speech Improvement Department of New York City functions in these three essential activities and to point out the main obstacles.

Thirty-eight special teachers of speech improvement serve 262 of the elementary and junior high schools. In addition to these, 199* teachers of elocution function in the high schools. The reorganization of the work of the special teachers of speech improvement is now in process. When it is completed, it is our hope that we shall have a large enough staff so that there will be one special teacher for each ten elementary and junior high schools. This teacher will be assisted in each school by a regular member of the staff, who has had some speech training and who is freed for at least three hours a week to conduct this work. The special teacher of speech

improvement will visit each school for an entire day every week. At the time of her visit she diagnoses all new cases and outlines a two-week program. In the presence of the assistant teacher, the specialist gives a demonstration of the type of work to be done with each child for the ensuing two weeks.

Upon subsequent visits to the school the special teacher examines each student, checking and modifying the program for an additional two-week period.

In conference with her assistant, the specialist outlines measures for securing cooperation with the school and the home and also arranges through the Department of Speech Improvement for such additional psychiatric, social service, medical, surgical or psychologic assistance as seems to be required.

The special teacher of speech improvement endeavors to enlist the intelligent cooperation of the teachers of the school by individual interviews with teachers who have charge of students exhibiting very difficult speech patterns. The specialist is also alive to the need for vocational and educational guidance for the speech handicapped. She cooperates with the guidance counsellors in the schools which she visits.

The department cooperates with the senior high schools in the matter of transferring permanent records of the speech cases and also in sending lists of entering students who require special speech care to the principals of senior high schools.

When the program has finally been worked out, it is hoped that in addition to her work for the handicapped, the special teacher of speech improvement will devote at least two hours of her visit to each school in supervision of the speech work for the normal children.

Classification of Speech Disorders According to Cause

While most cases are too complex to fall exclusively in any one classification, for the purpose of discussion it seems wise to divide our patients into three large and overlapping groups: first, those having speech defects with an organic basis, such as cleft palate, tongue-tie, deviate septum, paralysis, impaired hearing; second, purely functional disorders (although probably each of these has at least a slight organic or psychologic basis). Commonest among this type are nonorganic lisping, baby talk, bad voice production. The third group comprises persons having a psychologic or emotional imbalance in which the speech symptom is part of the entire personality picture. Of this type, stammering or stuttering, neurotic hoarseness, and hysterical mutism are perhaps the commonest.

Our treatment of these three cases follows closely upon the diagnosis of primary cause. For our organic defects we seek the aid of the specialist in oral surgery, orthodontia, and otology, as indicated. When the child has been brought to his optimum condition, a program of phonetic reeducation is begun. The matters of vocational guidance, school adjustment, health program are also considered. For the functional disorders a careful examination is made to eliminate the possibility of organic disturbance. The absence of any organic basis is then dramatized as motivation for effort in the speech correction program. Phonetic reeducation is then employed, including ear training, imitation of the sound, exercises for correct production, and directed drill.

In the psychologic cases we endeavor to discover and, so far as possible, eliminate, those physiologic, mental, or social factors which are militating against integration of the personality and a feeling of adequacy. The program includes positive health plans, mental hygiene, adjustment of the school and recreational program to the needs of the individual, and, in the speech clinic, a reconditioning of the attitude toward speech.

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*This figure does not include the 15 first assistants.

The Chief Obstacles to Success

The most obvious limitation to the work of speech improvement is due to the serious inadequacy of our staff. There are 632 elementary and junior high schools, only 262 of which are served by the teachers of speech improvement. These schools represent a sampling of the city's schools, and there is no reason to believe that fewer cases are to be found in those schools than those now visited.

In 1936, 27,206 students were treated in the speech clinics. It is safe to assume, then, that an additional 54,412 are not being helped in this vital matter of social adjustment.

A program of slow but steady extension is now under way, and we hope that by 1942 the number of speech improvement teachers will be sufficient to carry through our program of one teacher for each ten schools.

In the meanwhile, the department strives to augment its inadequate resources by conferences with parents held in the office of the director and by the establishment and conduction of two after-school clinics by members of the department, in conjunction with teacher-training courses.

Another serious obstacle to success is the ignorance and inertia, now, happily, on the wane, of administrators, educators, members of the medical profession, social workers, parents, and the general public in the matter of the seriousness and complexity of speech disorders.

This unawareness of the need for definite speech rehabilitation at an early age continues to handicap the lives of thousands of otherwise normal persons in our city. Adults who have had years of failure in speech situations are constantly applying to the office for assistance. The speech correction people may differ on various phases of the reeducation program, but they are as one in saying that early discovery is essential for rapid and positive correction. There seems to be no data to confirm the too common generalization on the part of family doctors that the children will "outgrow" their defects.

A third menace to the effective work of a program of rehabilitation is the number of charlatans who conduct private schools and advertise sure cures.

The American Speech Correction Association has a list of reputable speech correctionists in every region of the United States. The physician or parent who wishes to secure the services of a reputable person may do so by writing to the president of the American Speech Correction Association, Professor Lee Edward Travis, of the University of Iowa, Iowa City, Iowa, for accurate information about teachers in their various geographic locations.

What Can Be Done to Help

The general public needs to be educated as to the serious consequences of an uncorrected speech handicap. It should become a cause of social ostracism to ridicule a person whose speech is abnormal. Second, doctors, social workers, vocational counsellors, and others who give advice to parents should urge them to secure the assistance of a trained speech correctionist as soon as the difficulty manifests itself. Third, the parents and teachers of these students should familiarize themselves with the literature in the field so that they may cooperate intelligently with the speech specialist in the reeducation program. Fourth, pediatricians should familiarize themselves with the etiology of the commonest speech disorders and use their professional influence to persuade parents to avail themselves of special speech service, either in the public schools or, if that is not possible, among private teachers.

DISCUSSION

Several Questions

1. Dr. Blanton, we have noticed a good many children with speech disorders who seem to have some hyperthyroid condition. When this was cleared up, the speech

difficulty disappeared. Has it been your experience that glandular difficulties like this cause speech disorders?

2. I had a speech defect when I was a child. I went to a speech school and was placed on silent treatment for two weeks. This seemed to help me although it was very hard. Do you think such methods are helpful?

3. I have noticed several children with speech defects due to birth injuries. I think that the studies that Dr. Carlson and others have made have shown that there are probably new nervous pathways from the brain to the speech organs developed. Do you think so?

Answers

1. I have never seen speech disorders caused by glandular difficulties except of course hypothyroid states that cause mental retardation, the speech defect being a part of the mental retardation.

2. The silence treatment, if it is effective, is due to its suggestive influence. It is used by some of the schools for stutterers at the present time, but I would not advocate it.

3. I cannot answer this question. Perhaps Dr. Chesher can do it.

DR. B. M. JOSEPH (JERSEY CITY, N. J.).—Do you think that thumb-sucking and masturbation might be the cause of stuttering?

CHAIRMAN BLANTON.—Thumb-sucking and masturbation are infantile types of erotic pleasure. A certain amount of thumb-sucking and masturbation seems to be entirely normal. If a child was found to be sucking his thumb or masturbating to an excessive extent, we should feel that they were symptoms of some underlying pathologic condition. In a child who was given to excessive thumb-sucking and masturbation, there might also be stuttering, but we should feel that all three conditions, thumb-sucking, masturbation and stuttering were due to some deeper cause.

DR. B. S. VEEDER (ST. LOUIS).—Do you think a child might stutter because of imitation. I had a child some time ago whose stuttering seemed to be due to an imitation of his father, who had a slight stutter.

CHAIRMAN BLANTON.—Yes, children very often stutter because some member of the family stutters, but we should call this identification with the parent rather than imitation. A child imitates or identifies himself with some one only when there is some emotional relationship. In the case of a child who imitates another child who stutters, we believe that such imitation would not occur unless the child had some emotional relationship with the child that he was imitating.

DR. BERT I. BEVERLY (CHICAGO).—Where can we find places for training teachers of speech correction?

CHAIRMAN BLANTON.—The American Speech Correction Association, an organization of teachers and physicians, have organized training centers in the various universities where teachers of speech correction may receive instruction in speech training and mental hygiene. There are such training centers in the University of Wisconsin, University of Iowa, Teachers College of Columbia University, University of Michigan, University of Southern California, University of Louisiana, and other places.

DR. MARGARET R. REYNOLDS (JACKSON HEIGHTS, N. J.).—Do you think that we are justified in using sedative drugs in young children who have a severe stutter?

CHAIRMAN BLANTON.—Yes, I think we are justified in using sedative drugs for a short period of a few weeks or so in the case of nervous overactive children with a severe stutter.

DR. S. A. COHEN (NEW YORK CITY).—What can you do to develop normal speech?

CHAIRMAN BLANTON.—I think speech will be developed in any normal child who hears people talking in a normal way around him. I believe, however, that speech will be developed earlier and a larger vocabulary will be acquired if the mother talks to the child a great deal; even though she says things that he cannot understand, he gets the rhythm of her speech and is stimulated to try to talk back. If during the first two years of life the mother will name the toilet articles, such as brush, soap, and shoes, and things on the table, as bread, butter, etc., the child will very soon pick up these words.

DR. CHARLES BRADLEY (PROVIDENCE, R. I.).—We have a group of children in a hospital in Providence, R. I., and we find that about 60 per cent of them have a lack of dominance in the brain areas, and yet very few of them stutter. How do you account for it?

DR. CHESHER.—It is not Dr. Orton's belief that all children who lack dominance will stutter or have a speech defect. There must be a lack of dominance plus other factors. It is very complicated.

DR. C. L. LAMAR (BIRMINGHAM, ALA.).—At what age should speech correction be started in children who stutter?

DR. RAUBICHECK.—The training should be started as soon as the child begins to stutter, and this training, as Dr. Blanton has said, consists in modification of the child's environment.

CHAIRMAN BLANTON.—I do not believe that any speech correction should be used at an early age—only changes made in the child's environment.

MATTHEW WINTER, Secretary.

Indianapolis, Ind.

Academy News

The following physicians were elected to membership since the Seventh Annual Meeting of the Academy:

Region I

Dr. Herbert L. Elias, Rockville Center, Long Island, N. Y.
Dr. Margaret E. Fries, New York, N. Y.
Dr. Lendon Snedeker, Boston, Mass.
Dr. Hugh C. Thompson, Jr., Albany, N. Y.

Region II

Dr. J. W. Hayes, Jacksonville, Fla.
Dr. W. D. Mims, Memphis, Tenn.
Dr. Charles F. Rennick, El Paso, Tex.

Region III

Dr. Merlin Cooper, Cincinnati, Ohio